ERG Final

Economic Impact Studies: Blend Uniformity Analysis

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EXECUTIVE SUMMARY

On March 28, 2002, Product Quality Research Institute (PQRI) submitted to FDA its draft blend uniformity analysis recommendations developed by its Blend Uniformity Working Group (BUWG). The recommendations define the use of an alternative methodology for routine blend sampling that ensures the adequacy of mixing as required in 21 CFR 211.110(a)(3). More specifically, BUWG recommends stratified sampling and testing of in-process dosage units to demonstrate the uniformity of all production batches in lieu of routine sampling and testing of the blend.

Under contract to FDA, Eastern Research Group, Inc. (ERG) conducted a study of the costs and savings that would result from the adoption of BUWG recommendations by the pharmaceutical industry. Most of the industry data used in the study comes from two main sources: (1) an ERG telephone/mail survey of solid oral drug product manufacturers, and (2) the BUWG survey of industry practices. ERG also utilized available published literature on issues related to blend uniformity testing, perceived benefits of adopting the BUWG recommendations, and other relevant industry statistics. Where data were lacking, ERG employed additional assumptions and forecasts, as appropriate, to extrapolate variables of interest.

Using information from FDA's Orange Book database and additional data sources, such as the membership lists of Pharmaceutical Research and Manufacturers of America (PhRMA) and Generic Pharmaceutical Association (GPhA), ERG estimated that the BUWG proposal will affect the 218 firms that manufacture at least one solid oral drug product. For analysis purposes, ERG further classified 45 percent of these firms as innovator and the remaining 55 percent as generic manufacturers. The stratification was necessary because firms that predominantly manufacture generic drugs differ from their innovator counterparts in various aspects, such as average per-firm revenues, number of routine production batches, and number of unique

(A)NDAs. Further, while all generic manufacturers currently conduct blend uniformity testing on their routine production batches, manufacturers of most new (innovator) drugs have ceased routine blend testing of their commercial batches. These differences necessitate an analysis of economic impacts by type of firm, generic and innovator.

Based on discussions with FDA and drug manufacturers (generic and innovator), the tighter BUWG requirements for validation batches will impose incremental costs on all manufacturers. Further, all manufacturers will incur one-time costs to modify their manufacturing tickets and sample handling logistics. They will also incur costs to plan and coordinate the incorporation of these changes into their production operations. The tighter BUWG requirements for validation batches are, however, expected to improve total process and blending operation control which, in turn, will lead to fewer problems (i.e., fewer out-of-specification batches, product recalls) during manufacturing. Additionally, given the inherent sampling error associated with thief sampling of blends, the elimination of routine blend sampling will entirely eliminate out-of-specification (OOS) results arising from blend sampling errors. Thus, all drug manufacturers will accrue benefits from reductions in OOS batches. Moreover, manufacturers of generic drugs will realize additional savings with the elimination of routine blend testing of commercial batches.

Because pharmaceutical companies have not fully implemented the BUWG recommendations, the expected reduction in OOS result frequency must be forecast. Based on input from FDA personnel who have participated in the research and development of the BUWG recommendations, however, ERG judged that the implementation of the alternative methodology will entirely eliminate those OOS results that are due to blend sampling errors as well as those that are process related (particle segregation in the powder bed, incorrect mixing time, etc.). Because there is insufficient information on the share of OOS results due to nonprocess-related errors (i.e., human error, manufacturing equipment failure) among all OOS results, ERG estimated economic impacts under the following three scenarios:

- *Scenario 1 - 95 percent reduction in expected OOS result frequency*. This constitutes the best-case scenario where all OOS results that are not due to laboratory errors (estimated to comprise 5 percent of all OOS results) are process-related and hence are eliminated with the implementation of BUWG recommendations. This assumes that nonprocess-related errors are rare.

- *Scenario 2 - 90 percent reduction in expected OOS result frequency*. Under this scenario, all OOS results, except for laboratory errors (estimated at 5 percent of all OOS results) and nonprocess-related errors (forecast at 5 percent of all OOS results), are eliminated with the implementation of BUWG recommendations.

- *Scenario 3 - 80 percent reduction in expected OOS result frequency*. This constitutes the least optimistic scenario where all OOS results, except for laboratory errors (estimated at 5 percent of all OOS results) and nonprocess-related errors (forecast at 15 percent of all OOS results), are eliminated with the implementation of BUWG recommendations.

ERG estimated that the adoption of BUWG recommendations will result in net annual costs that range from $2,200 to $7,700 for small, from $11,700 to $44,000 for medium, and from $137,700 to $252,100 for large innovator firms. The generic firms, on the other hand, are estimated to realize net annual savings that range from $273,000 to $266,000 for small, from $1.2 million to $1.2 million for medium, and from $7.4 million to $7.3 million for large manufacturers (see Table E-1). ERG estimated the overall net annual savings to the solid oral drug product industry at $141.9 million under Scenario 3, $146.0 million under Scenario 2, and $148.0 million under Scenario 1 (see Table E-2). Under the BUWG proposal, the innovator firms are expected to incur incremental costs that range from $2.0 million to $4.1 million, mainly due to tightened testing requirements for validation. The generic industry, however, will realize cost savings of ranging from $146.0 million to $150.0 million.

Table E-1: Summary of Per-firm Economic Impacts from the Adoption of BUWG Recommendations Under Different Assumptions on the Expected Reduction in OOS Result Frequency, by Type of Firm

	Innovator			Generic		
Type of Cost (Saving)	**Small**	**Medium**	**Large**	**Small**	**Medium**	**Large**
Scenario 1 - 95% reduction						
Per-firm one-time costs (savings)	$6,673	$26,380	$84,810	$7,654	$25,072	$141,001
Per-firm recurring costs (savings)	$1,214	$7,902	$125,604	($274,108)	($1,218,147)	($7,468,647)
Per-firm annual costs (savings) [a]	$2,164	$11,658	$137,679	($273,018)	($1,214,577)	($7,448,572)
Scenario 2 - 90% reduction						
Per-firm one-time costs (savings)	$6,673	$26,380	$84,810	$7,654	$25,072	$141,001
Per-firm recurring costs (savings)	$3,070	$18,818	$163,753	($271,781)	($1,207,857)	($7,403,573)
Per-firm annual costs (savings) [a]	$4,020	$22,574	$175,828	($270,692)	($1,204,287)	($7,383,498)
Scenario 3 - 80% reduction						
Per-firm one-time costs (savings)	$6,673	$26,380	$84,810	$7,654	$25,072	$141,001
Per-firm recurring costs (savings)	$6,782	$40,651	$240,050	($267,129)	($1,187,278)	($7,273,425)
Per-firm annual costs (savings) [a]	$7,732	$44,407	$252,125	($266,039)	($1,183,708)	($7,253,350)

[a] The annual costs are equivalent to the sum of one-time costs annualized over a 10-year horizon using a 7 percent discount rate and recurring costs.

Table E-2: Summary of Total Economic Impacts from the Adoption of BUWG Recommendations Under Different Assumptions on the Expected Reduction in OOS Result Frequency , by Type of Firm

	Innovator				Generic				
Type of Cost (Saving)	**Small**	**Medium**	**Large**	**Total**	**Small**	**Medium**	**Large**	**Total**	**Total**
Scenario 1 - 95% reduction									
Per-firm one-time costs (savings)	$506,866	$278,982	$1,029,487	$1,815,335	$703,072	$320,645	$2,069,825	$3,093,542	**$4,908,877**
Per-firm recurring costs (savings)	$92,188	$83,564	$1,524,682	$1,700,434	($25,178,954)	($15,578,799)	($109,635,795)	($150,393,549)	**($148,693,115)**
Per-firm annual costs (savings) [a]	$164,355	$123,284	$1,671,258	$1,958,897	($25,078,853)	($15,533,147)	($109,341,098)	($149,953,098)	**($147,994,201)**
Scenario 2 - 90% reduction									
Per-firm one-time costs (savings)	$506,866	$278,982	$1,029,487	$1,815,335	$703,072	$320,645	$2,069,825	$3,093,542	**$4,908,877**
Per-firm recurring costs (savings)	$233,188	$199,011	$1,987,759	$2,419,958	($24,965,261)	($15,447,204)	($108,680,544)	($149,093,010)	**($146,673,051)**
Per-firm annual costs (savings) [a]	$305,355	$238,732	$2,134,335	$2,678,421	($24,865,160)	($15,401,552)	($108,385,848)	($148,652,559)	**($145,974,138)**
Scenario 3 - 80% reduction									
Per-firm one-time costs (savings)	$506,866	$278,982	$1,029,487	$1,815,335	$703,072	$320,645	$2,069,825	$3,093,542	**$4,908,877**
Per-firm recurring costs (savings)	$515,188	$429,906	$2,913,914	$3,859,008	($24,537,875)	($15,184,014)	($106,770,043)	($146,491,932)	**($142,632,924)**
Per-firm annual costs (savings) [a]	$587,354	$469,627	$3,060,489	$4,117,471	($24,437,773)	($15,138,362)	($106,475,346)	($146,051,481)	**($141,934,010)**

[a] The annual costs are equivalent to the sum of one-time costs annualized over a 10-year horizon using a 7 percent discount rate and recurring costs

SECTION ONE

INTRODUCTION

On March 28, 2002, PQRI's Blend Uniformity Working Group (BUWG) submitted its blend uniformity analysis recommendations to FDA. The recommendations concern the use of an alternative methodology to routine blend sampling to ensure adequacy of mixing as defined in 21 CFR 211.110(a)(3). More specifically, BUWG recommended the use of stratified sampling and testing of in-process dosage units to demonstrate the uniformity of all production batches in lieu of sampling and testing of the blend.

Section 1.1 describes the background on the blend uniformity issue and Section 1.2 outlines the BUWG recommendations. The data collection methodologies employed in the study are described in Section 1.3. Finally, Section 1.4 presents the economic impact estimation methodology, including labor valuations and the estimation of laboratory testing costs.

1.1 Background

Blend uniformity is addressed in Current Good Manufacturing Practices (cGMPs) regulations and drug approval programs. Section 211.110 of cGMPs requires drug manufacturers to establish "control procedures ... [that] include ... adequacy of mixing to assure uniformity and homogeneity." This requirement applies whenever mixing is performed in the manufacturing process. The cGMP regulations, however, do not specify the blend testing approach for the evaluation of batch uniformity. Further, the regulations do not prescribe the particulars, i.e., equipment, amount, and locations, acceptance criteria, limits, or significance levels of testing results (Timmermans, 2001).

Despite the lack of specificity in the regulations, the generic drug industry has been performing blend testing since the early 1990s on every commercial batch to demonstrate adequacy of mix under cGMPs. Additionally, some generic drug manufacturers have been submitting their blend test data to FDA as part of their Abbreviated New Drug Applications (ANDAs). The practice is mainly attributable to the 1993 ruling issued by Judge Wolin on the *United States v. Barr Laboratories* court case, commonly referred to as the Barr ruling. This decision has increased the awareness of both FDA inspectors and drug manufacturers of unacceptable quality control testing practices, lack of adequate failure investigations, and inadequate process validation (Jimenez, 1997). The ruling has also formed the legal foundation for FDA's enforcement of blend uniformity sampling requirements.

On August 27, 1999, in response to the significant variation in blend testing information submitted in ANDAs and the variability in FDA reviewers' expectations, FDA announced the availability of a draft guidance for industry titled "ANDAs: Blend Uniformity Analysis." The draft guidance provided recommendations to sponsors on the information to be provided in ANDAs for solid oral drug products on (1) bioequivalence and demonstration batches; and (2) in-process acceptance criteria related to blend testing. The draft guidance also specified the necessary sample sizes, number of sampling locations, acceptance criteria, and evaluation of test results and prescribed blend uniformity testing on every commercial batch. The guidance also left open the possibility of extending the requirements to NDA products. The draft guidance also indicated FDA's intention to seek the support of the PQRI on blend uniformity, and to update the guidance based on the outcome of any research.

After the release of the draft guidance, FDA received numerous comments from stakeholders. Comments reflected an industry-wide concern on the use of routine blend testing to demonstrate adequacy of mix under cGMPs and the limitations of current blend testing, sampling methodologies, and criteria. Both generic and innovator drug manufacturers provided such comments (Timmermans, 2001). As a result of the industry feedback, PQRI formed the BUWG and subsequently directed it to investigate this issue and generate potential solutions or alternatives.[1] Additionally, FDA withdrew the draft guidance and collaborated with PQRI in the blend uniformity research.

1.2 BUWG Recommendations on Blend Uniformity

After a 2-year effort on March 28, 2002, BUWG submitted its blend uniformity recommendations to FDA. BUWG recommended an alternative methodology for routine blend sampling to ensure adequacy of mixing. More specifically, BUWG suggested replacing routine sampling and testing of the blend with stratified sampling and testing of in-process dosage units to demonstrate the uniformity of all production batches (Massa, 2002). Under the recommendations, however, the amount of testing required to satisfy the cGMP requirements depends on the quality of data generated by testing the batches (exhibit, validation, and routine production) in accordance with the proposed strategy. For those products that readily comply with the BUWG acceptance criteria, BUWG suggests that a modified version of the U.S. Pharmacopeia (USP) Content Uniformity Test (USP, <905>) will satisfy the cGMP requirement for adequacy of mix for routine monitoring of production batches. Processes that do not readily comply will require additional testing for routine production batches (PQRI/BUWG, 2002).

For ANDA exhibit and process validation batches, BUWG recommends both blend and in-process dosage unit sampling according to the sampling plan depicted in Table 1-1. The manufacturer of the ANDA product is required to identify the appropriate sampling locations prior to the manufacture of the exhibit and/or validation batch. The manufacturer is then to assay the blend and in-process dosage unit samples. In the event of blending problems, BUWG

[1] PQRI is a nonprofit organization consisting of members of industry, government, and academia. The mission of PQRI is to conduct research to generate scientific information to support regulatory policy and help identify the types of product quality information that should be submitted in a regulatory filing to CDER (PQRI, 2003).

recommends further process development. Appendix A describes the BUWG recommendations by which manufacturers must demonstrate adequacy of mix and content uniformity for ANDA exhibit and validation batches.

Table 1-1: Sampling Plans for ANDA Exhibit and Process Validation Batches

Blend	Dosage Unit
Identify at least 10 locations in the blender from which to pull blend samples. Locations must be carefully chosen to represent potential areas of poor blending. For example, in tumbling blenders (such as V-blenders, double cones, or drum mixers), samples should be selected from at least 2 depths along the axis of the blender. For convective blenders (such as a ribbon blender), a special effort should be made to implement uniform volumetric sampling, including the corners and discharge area (at least 20 locations are suggested to adequately validate convective blenders). Take at least 3 replicate samples from each location.	Identify at least 20 locations throughout the compression or filling operation to obtain dosage units. The sampling locations must be carefully chosen to represent significant events (e.g., hopper changeover) during the compression or filling process including samples from the beginning and end of the compression or filling operation. Take at least 7 dosage units from each location.

Source: PQRI/BUWG, 2002

For routine production batches, BUWG recommends in-process dosage unit analysis in lieu of blend *and* compendial testing. To utilize this method, however, manufacturers must demonstrate that testing of in-process stratified dosage unit samples provides at least equivalent control (i.e., sensitivity to lack of uniformity) to compendial testing of finished dosage units for each ANDA exhibit and validation batch. Upon demonstration of such a relationship, the BUWG recommendations allow the manufacturer to cease compendial testing all together for demonstrating Uniformity of Dosage Units by Content Uniformity. If the relationship between in-process and compendial testing cannot be demonstrated as proposed, then the manufacturer is required to conduct both in-process stratified and finished product compendial testing.

BUWG specifies different testing methodologies as well as a switching regime between testing methods for “readily-compliant” and “marginally-compliant” routine production batches to demonstrate adequacy of mix and content uniformity (see Appendix B). Under the recommendations, products with relative standard deviation (RSD) values of less than or equal to 4.0 percent for in-process dosage units of each exhibit and validation batch (with all mean results falling within 90.0 and 110.0 percent and all individual results between 75.0 and 125.0 percent), are considered readily compliant. Products yielding marginal results (i.e., at least one of the exhibit or validation batches have an RSD value greater than 4.0 but less than or equal to 6.0 percent for in-process dosage units) are considered marginally compliant. BUWG recommends additional testing of in-process dosage units for marginally compliant batches, as depicted in Appendix B.

1.3 Data Collection Methodology

Most of the industry data used in the economic analysis comes from two main sources: (1) an ERG survey of drug manufacturers and (2) the BUWG survey of industry practices. ERG also used available published literature on issues related to blend uniformity testing and perceived benefits of adopting the BUWG recommendations.

ERG conducted a small telephone survey of solid oral drug product manufacturers.[2] The survey elicited information on current blend uniformity practices, including the number of samples taken and analyzed, sampling costs, and types of analytical tests performed. Companies were also asked to provide information on (1) various company characteristics (employment size, number of solid oral drug products manufactured, number of validation and routine production batches produced per annum, and average value per batch) and (2) forecasts of costs/savings, if any, under BUWG recommendations. To minimize the reporting burden on companies, the survey requested most data on a "representative" batch basis, where a representative batch was defined as one that adequately characterized the majority of batches manufactured by the

[2] Although a mail questionnaire was prepared, telephone interviews proved to be more effective in eliciting company responses. One company, however, also completed the mail questionnaire.

responding company. ERG had telephone conversations with executives of two generic and two innovator companies. These discussions were with executives in the Statistics and Product Quality departments of these companies. ERG also used the results of the BUWG survey of current industry practices to supplement the data generated by the ERG survey. Because ERG did not have access to the survey database of individual responses, however, separate tabulations by company size were not compiled.

1.4 Economic Impact Estimation Protocols

This section presents the protocols used in estimating the economic impacts of BUWG recommendations on solid oral drug manufacturers, including labor valuations and laboratory testing costs. Some companies contacted indicated having adopted a modified version of the BUWG recommendations for validation. None of the companies indicated using the methodology described in the BUWG proposal for routine production, however. Overall, the majority of companies contacted did not have any concrete experience in in-process content uniformity testing and lacked any forecasts of net savings/cost impacts associated with BUWG recommendations. Thus, ERG employed additional assumptions and estimates, as appropriate, to extrapolate incremental economic impacts. Section Three discusses all assumptions and extrapolations used in the economic impact estimation in further detail.

1.4.1 Labor Valuations

ERG used occupational wage data published by the Bureau of Labor Statistics (BLS) to value manufacturer labor hours. The reported wage rates were inflated by 37.6 percent (which is the ratio of total benefits to wages and salaries reported by the BLS) to reflect fringe benefits (BLS, 2002). Table 1-2 presents the wage rates used for various labor categories in the economic impact analysis.

Table 1-2: Wage Rates Used in Labor Valuation Calculations

Type of Personnel	Applicable SOC Code [a]	Mean Hourly Wage	Fringe [b]	Mean Hourly Wage and Fringe [c]
Production operator	51-9023: Mixing and Blending Machine Setters, Operators, and Tenders	$13.36	$5.02	$18.38
Laboratory technician	29-2012: Medical and Clinical Laboratory Technicians	$14.52	$5.45	$19.97
Statistician	15-2041: Statisticians	$27.44	$10.31	$37.75
Mid-level manager	11-3051: Industrial Production Managers	$32.84	$12.34	$45.18
Manager	11-1021: General and Operations Managers	$35.37	$13.29	$48.66

Source: BLS, 2001 and BLS, 2002

[a] Refers to the 7-digit Standard Occupational Classification (SOC) code for the occupation in data provided by the Bureau of Labor Statistics.

[b] Estimated at 37.6 percent of the reported mean hourly wage rate.

[c] Computed as the sum of mean hourly wage and fringe benefits.

1.4.2 Laboratory Testing Costs

The most common laboratory procedures used in testing dose uniformity include, but are not limited to, liquid chromatography (HPLC), thin layer chromatography, gas chromatography, infrared spectroscopy, and atomic absorption spectroscopy. Most large pharmaceutical companies have in-house laboratories where these tests are conducted. Smaller drug manufacturers and start-up companies, however, may use outside testing laboratories.

To estimate the per-sample dose uniformity testing costs, ERG obtained price quotes for the various procedures commonly used from its own testing laboratory in Morrisville, NC, as well as an independent testing laboratory serving the pharmaceutical industry. Table 1-3 presents these per-sample testing costs by type of procedure and by source. ERG estimated the per-sample testing cost by procedure by averaging the two reported prices and deflating the result by 30 percent to reflect scale economies from frequent testing.[3]

[3] The 30 percent price discount is based on the reported volume discount by ChemTest Laboratories (ChemTest Laboratories, 2003).

Table 1-3: Active Ingredient Analysis Testing Costs

Type of Test	Laboratory 1 [a]	Laboratory 2 [b]	Average [c]
Active ingredient assay	$600 to $1,200	$75	$446
Infrared Spectroscopy	$50 to $75	$75	$44
Liquid Chromatography (HPLC)	$100 to $250	$200 to $250	$123
Thin Layer Chromatography	$75 to $150	$75	$79
Gas Chromatography	$100 to $250	$100 to $150	$123
Atomic Absorption Spectroscopy	$53 [d]	NA	$37
Ultraviolet/Visible Spectrum	$50 to $75	$75	$44
Average	**NA**	**NA**	**$128**

[a] ERG, 2003

[b] ChemTest Laboratories, 2003

[c] The figure corresponds to the midpoint of the reported range for the relevant test and incorporates an average 30 percent volume discount.

[d] The price is the sum of $35 for sample digestion and $18 per element testing costs.

From the table, the estimated per-sample testing costs range from $37 per sample for atomic absorption spectroscopy to as high as $446 per sample for an active ingredient assay. Given that there is insufficient information on the frequency of the different types of procedures companies use for dose uniformity testing, ERG estimated the overall analytical laboratory testing cost at $128 per sample, which is the simple average of per-sample testing costs by procedure. For the analysis, ERG judged that the laboratory testing cost by an independent laboratory specializing in testing services, is comparable to the cost of in-house testing at the margin.

SECTION TWO

INDUSTRY PROFILE

This section profiles the manufacturers of solid oral drug products affected by the BUWG recommendations. Section 2.1 provides the Small Business Administration (SBA) data on those North American Classification System (NAICS) industries within which most pharmaceutical manufacturers are classified. Section 2.2 presents the data on the number of solid oral drug product manufacturers compiled from various sources, such as FDA's Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, the company listing used for the BUWG survey, and membership listings of various trade associations. Finally Section 2.3 presents estimates of the number and other characteristics of companies impacted, by firm size and type (i.e., innovator and generic).

2.1 Small Business Administration (SBA) Data on Pharmaceutical Manufacturers

The SBA provides annual data on the number of firms, establishments, employment, and annual payroll by employment size class and NAICS industry. Manufacturers of pharmaceuticals are typically classified within the following two NAICS industries:

- NAICS 325411: Medicinal and botanical manufacturing, and
- NAICS 325412: Pharmaceutical preparation manufacturing.

As depicted in Table 2-1, the pharmaceutical industry consists of approximately 1,100 firms of which 77 percent are small with less than 100 employees, 11 percent are medium-sized with 100 to 499 employees, and the remaining 12 percent are large with more than 499 employees.

Table 2-1: SBA Data on Pharmaceutical Companies for Year 2000

Industry		Firms	Establishments	Employment	Revenues ($) [a]
NAICS 325411: Medicinal and Botanical Manufacturing					
[b] Small:	Less than 100 employees	255	260	3,867	$1,522,851,022
Medium:	100 to 499 employees	30	32	3,958	$1,774,532,313
Large:	More than 499 employees	36	53	20,308	$12,461,189,422
Total		321	345	28,133	15,758,572,757
NAICS 325412: Pharmaceutical Preparation Manufacturing					
[b] Small:	Less than 100 employees	571	573	9,089	$3,562,295,390
Medium:	100 to 499 employees	85	98	15,494	$6,839,060,120
Large:	More than 499 employees	96	235	111,371	$67,233,962,384
Total		752	906	135,954	77,635,317,894
All Industries					
[b] Small:	Less than 100 employees	826	833	12,956	5,085,146,412
Medium:	100 to 499 employees	115	130	19,452	8,613,592,433
Large:	More than 499 employees	132	288	131,679	79,695,151,805
Total		1,073	1,251	164,087	93,393,890,651

Source: SBA, 2000 and SBA, 1996

[a] Revenues determined by multiplying the 2000 number of employees by the ratio of revenue per employee in the 1996 SBA data.

[b] SBA classifies entities with more than 750 employees as small business for NAICS 325411 and 325412. For purposes of analysis, however, ERG defined businesses with less than 100 employees as small, with 100 and 499 employees as medium-sized, and with more than 499 employees as large. The redefined size classes better capture the differences among firms, such as average number of products, revenues, unique (A)NDAs, that are relevant for assessing economic impacts than the SBA definition.

Further, the average per-firm revenues of pharmaceutical companies range from $6.2 million for small to $74.9 million for medium-sized to $603.8 million for large companies.

2.2 Number of Affected Firms

Not all pharmaceutical companies manufacture solid oral drug products. To identify manufacturers of solid oral drug products, ERG utilized FDA's Orange Book database along with a number of additional data sources. According to the data compiled from the Orange Book, there are a total of 304 companies that have at least one solid oral drug product approved by FDA as of December 2002.[4] The data also indicate that the total number of solid oral drug products currently marketed in the US is approximately 6,000 (including all dosage strengths), which corresponds to around 3,700 unique (A)NDAs.

The FDA database, however, contains duplicate entries, possibly because it is only updated periodically, and does not depict the various parent-subsidiary relationships that exist among the companies listed. To determine the number of "firms" affected, where a firm is defined as the parent company, ERG utilized the company listing compiled by the BUWG for its survey of current industry practices (Boehm, 2003). Using this list and the list tabulated from the Orange Book database, ERG estimated the total number of firms that manufacture at least one solid oral drug product at 218. Further, using the membership lists of Pharmaceutical Research and Manufacturers of America (PhRMA) and Generic Pharmaceutical Association (GPhA), ERG estimated that around 45 percent of these companies are innovator manufacturers and the remaining 55 percent are generic manufacturers (PhRMA, 2003 and GPhA, 2003).[5] Assuming that the distribution of affected firms (innovator and generic combined) across size classes resembles that of the industry, ERG estimated that of the 218 firms, 168 are small, 24 are medium-sized, and 26 are large manufacturers. The stratification by size and type of company (generic versus innovator) is necessary for analysis purposes because firms differ in various aspects, such as average per-firm revenues, number of routine production batches, and number of unique (A)NDAs, within these two dimensions. Further, while all generic manufacturers currently conduct blend uniformity testing on their routine production batches, manufacturers of

[4] The figure includes all active (A)NDAs for prescription and over-the-counter drugs for which the dosage form field contains the phrase "tablet", "capsule", or 'tablet; capsule".

[5] Some pharmaceutical companies manufacture both innovator and generic drugs. For the purposes of the study, however, ERG classified a company as innovator or generic based on its trade association membership rather than its actual product composition. This was based on the assumption that those companies whose products are predominantly generic or are new drugs are likely to be members of GPhA or PhRMA, respectively.

most new (innovator) drugs have ceased routine blend testing of their commercial batches. These differences require separate assessments of economic impacts for each type of firm.

2.3 Estimates of the Number and Other Characteristics of Firms Affected by Size and Type

Table 2-2 provides the industry profile of firms compiled from various data sources. Where data were lacking, ERG employed additional assumptions to extrapolate estimates, as noted in the table. Some of these estimates, such as the number of validation and routine production batches and the expected frequency of out-of-specification (OOS) batches, are highly variable within, as well as between, firms.

The project consultant indicated that the scale of production can potentially vary from one batch per day for high-volume products to as low as 2 to 3 batches a year for low-volume products. Further, the number of validation batches manufactured per year could vary based on whether the company undertakes any (1) manufacturing site changes to better utilize production capacity, (2) process and/or equipment changes to improve yields or quality control, (3) composition and/or component changes in response to various production problems, and (4) scale-up or scale-down activities to better control production costs. For the analysis, ERG assumed that a given firm manufactures an average of 15 routine production batches per product, including all dosage strengths, and one validation batch per (A)NDA per year. This translates into a range of around 90 to 1,830 routine production batches per-firm for small to large innovator firms and around 110 to 3,110 for small to large generic firms. The average number of validation batches manufactured per year are then estimated at 3 for small firms to 73 for large innovator firms and 4 for small firms to approximately 136 for large generic firms. Because these figures significantly influence economic impacts, ERG conducted a sensitivity analysis to characterize the degree of uncertainty (see Section Four).

Table 2-2: Industry Profile of Solid Oral Drug Product Manufacturers

	Innovator			Generic			
Element	**Small**	**Medium**	**Large**	**Small**	**Medium**	**Large**	**Source/Comment**
Number of firms	76	11	12	92	13	15	Orange Book, 2003; Boehm, 2003; PhRMA, 2003; GPhA, 2003
Number of establishments	77	12	26	93	14	32	Computed by multiplying the SBA firm-establishment ratio by the number of firms
Revenues [a]	$6,156,352	$74,900,804	$603,751,150	$6,156,352	$74,900,804	$603,751,150	SBA, 2000 and 1996
Number of products [b]	6	35	122	7	33	208	Orange Book, 2002
Number of unique (A)NDAs	3	18	73	4	17	136	Orange Book, 2002
Number of validation batches per annum	3	18	73	4	17	136	Assumes an average of 1 validation batch per (A)NDA per annum
Number of routine production batches per annum	89	523	1,826	111	493	3,115	Assumes an average of 15 batches per product per annum
Average value ($) per batch	$69,292	$143,351	$330,658	$55,290	$152,083	$193,843	Computed by dividing the average revenues by the number of routine production batches
Weighted average value ($)		$94,782			$94,782		Computed as the weighted average of per-batch value, weights equal number of firms
Average production time (in hours) per batch	64	12	7	51	13	4	Assumes that there are 2 production shifts for 365 days per year per establishment
Weighted average production time (in hours)		46			46		Computed as the weighted average of per-batch manufacturing time where weights equal number of firms
% of production batches tested for blend uniformity	0.0%	0.0%	0.0%	100.0%	100.0%	100.0%	ERG estimate
Percentage reduction in OOS batch frequency							
Scenario 1	95%	95%	95%	95%	95%	95%	ERG estimate
Scenario 2	90%	90%	90%	90%	90%	90%	ERG estimate
Scenario 3	80%	80%	80%	80%	80%	80%	ERG estimate

[a] The per-firm revenues for innovator companies are expected to be higher than their generic counterparts. However, SBA does not report revenue figures separately for innovator and generic firms.
[b] The figure includes all approved solid oral drug product (A)NDAs, including all dosage strengths.

While it is not uncommon for some manufacturing facilities to have 3 shifts per day for 7 days a week, project consultants indicated that most operations run 2 shifts per day for 7 days a week. Thus, ERG estimated that an average facility operates for 5,840 hours a year (i.e., 8 hours/shift × 2 shifts × 365 days/year). This implies an average manufacturing time per batch of around 46 hours, computed by dividing the total manufacturing hours by the total number of batches manufactured (validation and routine production combined) by firm size and weighting them by the number of firms in each size class.

One of the uncertainties is the expected percentage reduction in OOS batch frequencies. The project consultant and the pharmaceutical companies contacted indicated that the BUWG recommendations will improve total process and blending operation control due to tightened testing during validation (Company 1 and 2, 2003). Companies also indicated that this is likely to lead to fewer problems (i.e, fewer OOS batches, product recalls) during manufacturing. Additionally, given the inherent sampling error associated with thief sampling of blends, companies noted that the elimination of routine blend sampling will entirely eliminate OOS results arising from blend sampling errors (Company 3 and 4, 2003). Because pharmaceutical companies have not fully implemented the BUWG recommendations, however, most companies were unable to forecast, with much certainty, the expected reduction in OOS batch frequencies with the full adoption of the BUWG recommendations. Thus, ERG evaluated economic impacts under three different assumptions on the expected reduction in OOS result frequency due to the adoption of BUWG recommendations. For the best-case scenario (Scenario 1), ERG forecasted that all OOS results that are not due to laboratory errors (estimated at 5 percent of all OOS results) are eliminated with the implementation of BUWG recommendations (i.e., 95 percent reduction in OOS result frequency). To accommodate the possibility that some nonprocess-related errors (i.e., human error, manufacturing equipment failure) may still occur in addition to the laboratory errors after the adoption of BUWG recommendations, ERG forecasted 90 and 80 percent reductions in OOS result frequency for the remaining two scenarios 2 and 3, respectively.

Given the uncertainty surrounding the estimate, ERG also conducted a separate analysis depicting the sensitivity of economic impact estimates to this variable (see Section Four).

SECTION THREE

ECONOMIC IMPACTS

This section presents the economic impacts of adopting blend uniformity analysis recommendations of BUWG on solid oral drug product manufacturers. Section 3.1 outlines the assumptions and parameters used in modeling current industry practices and how firms will adjust their practices to meet the BUWG recommendations. The section addresses blend testing, compendial testing, in-process content uniformity (CU) testing, and out-of-specification (OOS) result analysis that are relevant to the analysis of economic impacts. Section 3.2 discusses the one-time costs for incorporating the BUWG recommendations into their operations. Finally, Sections 3.3 and 3.4 present the unit and total impacts on affected firms by type and size, respectively.

3.1 Model Assumptions and Parameters

ERG modeled the applicable costs companies incur in the baseline (i.e., current practice) and are expected to incur after adopting the BUWG recommendations separately for validation and routine production batches. For validation batches, companies currently incur costs to meet blend and compendial testing requirements. With the adoption of BUWG recommendations, companies will also need to conduct in-process content uniformity (CU) testing (in addition to blend and compendial testing) on their validation batches. For routine production batches, companies currently incur costs for blend and compendial testing, as well as for resolving out-of-specification (OOS) results. Under the BUWG proposal, companies will need to conduct in-process CU testing in lieu of blend and compendial testing but will still incur costs to investigate and resolve any OOS results encountered during production.[6] Hence, in the analysis, ERG computed the applicable baseline costs, i, and costs after the adoption of BUWG recommendations, j, per validation and routine production batch as follows:

Current Practice (*i*)

$$TC_{vi} = BT_{vi} + CT_{vi}$$

$$TC_{ri} = BT_{ri} + CT_{ri} + p_{OOSi} \times OOS_i$$

BUWG Recommendation (*j*)

$$TC_{vj} = BT_{vj} + CT_{vj} + ICUT_{vj}$$

$$TC_{rj} = p_{CTrj} \times CT_{rj} + ICUT_{rj} + p_{OOSj} \times OOS_j$$

where

r = Routine production batch,

v = Validation batch,

TC = Total economic cost per batch,

BT = Blend testing cost per batch,

CT = Compendial testing cost,

$ICUT$ = In-process content uniformity testing cost,

OOS = Out-of-specification analysis and resolution cost,

[6] As noted in Section One, companies that fail to demonstrate a relationship between in-process and compendial test results will need to conduct both in-process CU *and* compendial testing under the BUWG proposal. In the model, ERG assumed that manufacturers will need to conduct both tests for only 5 percent of their products. ERG judged that manufacturers will be able to demonstrate equivalency for the majority (95 percent) of their products.

p_{CT} = Expected probability of compendial testing in addition to in-process content uniformity testing, and

p_{OOS} = Expected probability of an OOS result.

ERG then computed the net economic impact of adopting the BUWG recommendations as the difference between the costs under current practice and those companies will incur under the BUWG proposal for validation and routine production batches. Table 3-1 presents the assumptions and parameters used in computing annual baseline costs and costs under the BUWG proposal per validation and routine production batch. The one-time costs companies will incur to adopt the BUWG recommendations are addressed in Section 3.2.

3.1.1 Blend Testing

For blend testing, firms collect small samples from a static powder bed and assay them to assess content uniformity. The main goal of blend testing is to demonstrate the adequacy of mix as required under 21 CFR 211.110(a)(3). Although a minority of pharmaceutical companies use automated blend sampling and testing, such as Near Infrared Spectroscopy (NIR), the majority use traditional labor-intensive method of sampling with a thief (i.e., a long sampling tool).

According to the scientific literature and companies contacted, the thief might not be the ideal sampling device for collecting small representative samples from a large static powder bed (Company 4, 2003 and PDA, 1996). First, as it is inserted into a powder bed, a thief distorts the bed by carrying material from the upper layers towards the lower layers. Because appreciable force is necessary to insert the thief into a powder bed, unrepresentative samples can be collected due to compaction and particle attrition. Furthermore, the flow characteristics of the powder may bias the samples taken, with more freely-flowing powder collecting in the thief chambers. Finally, thief design and angle of insertion into a powder bed have been shown to influence sampling results (PDA, 1996). Overall, these factors make blend sampling prone to sampling

Table 3-1: Model Assumptions and Parameters

	Current Practice		BUWG Recommendation		
Element	Validation	Routine Production	Validation	Routine Production	Source
Blend Testing	**$887**	**$2,497**	**$1,398**	**NA**	Computed value
Production operator hours to prepare for and obtain samples	6	2	6	NA	[a]
Production operator hourly wage rate	$18.38	$18.38	$18.38	NA	BLS 2002 and 2001
Laboratory testing cost per sample to demonstrate blend uniformity	$128	$128	$128	NA	ChemTest and ERG, 2003
Average number of samples tested for blend uniformity per batch	6	3	10	NA	PQRI/BUWG, 2002
Laboratory technician hours for recordkeeping	0.5	0.5	0.5	NA	[a]
Laboratory technician hourly wage rate	$19.97	$19.97	$19.97	NA	BLS 2002 and 2001
Average number of hours manufacturing equipment remains idle per batch	1	1	NA	NA	[a]
Average number of hours required to manufacture one production batch	NA	46	NA	NA	[a]
Average value of a representative batch	NA	$94,782	NA	NA	[a]
Revenue loss due to idle manufacturing equipment	NA	$2,067	NA	NA	[a]
Compendial Testing (USP <905>)	**$3,315**	**$1,325**	**$3,315**	**$66**	Computed value
Production operator hours to prepare for and obtain samples	6	2	6	2	[a]
Production operator hourly wage rate	$18.38	$18.38	$18.38	$18.38	BLS 2002 and 2001
Laboratory testing cost per sample to demonstrate dosage form uniformity	$128	$128	$128	$128	ChemTest and ERG, 2003
Average number of samples tested for dosage form uniformity per batch	25	10	25	10	USP <905>
Laboratory technician hours for recordkeeping	0.5	0.5	0.5	0.5	[a]
Laboratory technician hourly wage rate	$19.97	$19.97	$19.97	$19.97	BLS 2002 and 2001
Estimated percentage of affected batches that require compendial testing	100.0%	100.0%	100.0%	5.0%	[a]
In-process Content Uniformity (CU) Testing	**NA**	**NA**	**$7,761**	**$1,394**	Computed value
Production operator hours to prepare for and obtain in-process samples	NA	NA	4	2	[a]
Production operator hourly wage rate	NA	NA	$18.38	$18.38	BLS 2002 and 2001
Laboratory technician hours for recordkeeping	NA	NA	1	1	[a]
Laboratory technician hourly wage rate	NA	NA	$19.97	$19.97	BLS 2002 and 2001
Laboratory testing cost per sample to demonstrate uniformity	NA	NA	$128	$128	ChemTest and ERG, 2003

Table 3-1: Model Assumptions and Parameters

Element	Current Practice		BUWG Recommendation		Source
	Validation	Routine Production	Validation	Routine Production	
Average number of samples tested per batch	NA	NA	60	NA	PQRI/BUWG, 2002
Average number of samples tested per readily-compliant batch	NA	NA	NA	10	PQRI/BUWG, 2002
Expected probability for a readily-compliant batch	NA	NA	NA	97.7%	PQRI/BUWG, 2002
Average number of samples tested per marginally-compliant batch	NA	NA	NA	30	PQRI/BUWG, 2002
Expected probability of a marginally-compliant batch	NA	NA	NA	2.3%	PQRI/BUWG, 2002
Out-of-Specification (OOS) Analysis and Resolution	**NA**	**$20,893**	**NA**	**$20,893**	Computed value
Analysis & Resolution of Quickly-Resolved Problems (Laboratory Errors)	NA	$1,235	NA	$1,235	Computed value
Laboratory technician hours for OOS investigation and reporting	NA	20	NA	20	[a]
Laboratory technician hourly wage rate	NA	$19.97	NA	$19.97	BLS 2002 and 2001
Mid-level manager hours for review/approval of investigation report	NA	10	NA	10	[a]
Mid-level manager hourly wage rate	NA	$45.18	NA	$45.18	BLS 2002 and 2001
Average number of additional samples tested per batch	NA	3	NA	3	[a]
Laboratory testing cost per sample to demonstrate uniformity	NA	$128	NA	$128	ChemTest and ERG, 2003
Percentage of OOS results that are quickly resolved	NA	5.0%	NA	5.0%	[a]
Analysis & Resolution of Not-Quickly-Resolved Problems	NA	$21,928	NA	$21,928	Computed value
Laboratory technician hours for OOS investigation and reporting	NA	320	NA	320	[a]
Laboratory technician hourly wage rate	NA	$19.97	NA	$19.97	BLS 2002 and 2001
Statistician hours for data analysis	NA	80	NA	80	[a]
Statistician hourly wage rate	NA	$37.75	NA	$37.75	BLS 2002 and 2001
Mid-level manager hours for review/approval of investigation report	NA	40	NA	40	[a]
Mid-level manager hourly wage rate	NA	$45.18	NA	$45.18	BLS 2002 and 2001
Managerial hours for review and approval of investigation report	NA	10	NA	10	[a]
Managerial hourly wage rate	NA	$48.66	NA	$48.66	BLS 2002 and 2001
Percentage of OOS results that are not quickly resolved	NA	95.0%	NA	95.0%	[a]

Table 3-1: Model Assumptions and Parameters

Element	Current Practice Validation	Current Practice Routine Production	BUWG Recommendation Validation	BUWG Recommendation Routine Production	Source
Option 1: Repeat blend sampling and testing	NA	$484	NA	$484	Computed value
Blend testing cost (from above)	NA	$2,497	NA	$2,497	Computed value
Probability of option 1	NA	19.4%	NA	19.4%	BUWG, 2000
Option 2: Perform extended compendial testing of finished dosage	NA	$239	NA	$239	Computed value
Estimated at 50 percent of regular compendial testing costs	NA	$662	NA	$662	Computed value
Probability of option 2	NA	36.1%	NA	36.1%	BUWG, 2000
Option 3: Perform extended blend sampling and testing	NA	$625	NA	$625	Computed value
Estimated at 1.5 times the regular blend testing cost	NA	$3,745	NA	$3,745	Computed value
Probability of option 3	NA	16.7%	NA	16.7%	BUWG, 2000
Option 4: Remix blend and reconduct sampling and testing	NA	$553	NA	$553	Computed value
Production operator hours to remix blend	NA	2	NA	2	[a]
Production operator hourly wage rate	NA	$18.38	NA	$18.38	BLS 2002 and 2001
Average value of a representative batch	NA	$94,782	NA	$94,782	[a]
Average number of hours to manufacture one production batch	NA	46	NA	46	[a]
Revenue loss due to blending equipment use to remix blend	NA	$4,134	NA	$4,134	Computed value
Blend testing cost	NA	$2,497	NA	$2,497	Computed value
Probability of option 4	NA	8.3%	NA	8.3%	BUWG, 2000
Option 5: Reject the batch	NA	$5,308	NA	$5,308	Computed value
Average value of a representative batch	NA	$94,782	NA	$94,782	[a]
Probability of option 5	NA	5.6%	NA	5.6%	BUWG, 2000
Option 6 Other (unspecified)	NA	$3,012	NA	$3,012	Computed value
Average cost of all options (average of option 1 through 5 above)	NA	$21,671	NA	$21,671	Computed value
Probability of option 6	NA	13.9%	NA	13.9%	BUWG, 2000

[a] ERG estimate based on discussions with pharmaceutical companies and project consultant.

error. The potential for sampling errors further increases as the size of the sample and/or the concentration of the drug active substance(s) in the formulation decreases.

Upon achieving the proper mixing time, workers stop the blender to allow sampling. While one operator removes the samples from the blender, another places the collected samples into designated vials for transfer to the analytical laboratory (Company 1 and 4, 2003). Companies indicated that the process, including the time to assay the samples collected, can potentially range from 6 to as high as 30 hours per batch (Company 1 and 2, 2003). Although some companies may collect as much as 30 samples (Company 1, 2003), most companies collect 10 or fewer blend samples for testing per validation and per routine production batch (BUWG, 2000).

Current practice. ERG estimated the time required to prepare for and obtain blend samples at 6 hours per validation and 2 hours per routine production batch. During the sampling process, however, ERG judged the blending equipment typically remains idle for only an hour (the time it takes one operator to insert the thief into the powder bed and pull samples).[7] ERG further estimated that, on average, companies assay 6 samples per validation and 3 samples per routine production batch at a cost of $128 per sample (see Section 1.4.2). Given that it takes approximately half an hour to document and record the results of all assays, ERG computed the blend-testing cost per validation batch at $887. ERG did not allocate costs due to idle blending equipment time for validation batches.

During routine production, the equipment down time to accommodate sampling reduces efficiency (Company 2, 2003). Given that it takes roughly 46 hours to manufacture a single commercial scale batch with an estimated average value of $94,782, an hour of idle blending

[7] Some pharmaceutical companies have their own unique way of obtaining samples from a blender which may potentially take longer than one hour. Further, sampling hazardous powders may involve more time. ERG judged, however, that the one hour estimate is sufficient for most companies.

equipment time can be valued at $2,067 (i.e., $94,782 × 1/46) per routine production batch. Additionally, ERG estimated the cost of testing per routine production batch at $430. This cost consists of 2.5 labor hours to pull blend samples and record test results and $384 in laboratory testing costs ($128 × 3 samples). Overall, the baseline total cost of blend testing per routine production batch is estimated at $2,497 in the model.

BUWG Recommendation. For validation batches, BUWG recommends both blend and in-process dosage unit sampling according to the sampling plan provided in Table 1-1. BUWG recommends that manufacturers take 3 replicate samples per location from 10 locations for tumbling blenders (such as V-blenders, drum mixers, and double cone blenders) and from 20 locations for convective blenders (such as ribbon blenders). BUWG further directs manufacturers to assay at least one sample per location for blend uniformity.[8] Based on discussions with the project consultant, tumbling blenders are most common. Thus, ERG estimated that the majority of manufacturers will take 30 samples total and assay 10 per validation batch. Assuming that sampling and recordkeeping takes the same number of labor hours as before, ERG estimated the total cost of blend testing per validation batch under the BUWG proposal at $1,398.

There are no blend-testing requirements for routine production batches under the BUWG proposal. Thus, ERG did not allocate any costs for routine production batches.

3.1.2 Compendial Testing (USP <905>)

Under USP <905>, pharmaceutical manufacturers must demonstrate the uniformity of their solid oral drug products by assaying individual dosage units and applying the acceptance criteria specified. The content uniformity test, hereinafter referred to as compendial testing, is

[8] Based on the results of the first set of assays, some manufacturers might also need to assay the second and third samples per location and investigate the original criteria failure.

required for all coated tablets, transdermal systems, and suspensions in single-unit containers or in soft capsules that contain inactive or active added substances, except where the test for weight variation may be applied.[9] For the determination of dosage-form uniformity by assay of individual units under USP <905>, a manufacturer needs to sample at least 30 dosage units and assay 10 units. The USP chapter does not, however, specify (1) how these dosage units should be sampled (i.e., random versus stratified random) and (2) whether the sample can include in-process in addition to finished dosage forms. Hence, solid oral drug product manufacturers approach compendial testing in different ways. Some manufacturers randomly sample and assay only finished dosage forms while others also include in-process dosage forms.

Current practice. The compendial testing costs per batch vary between validation and routine production batches. One company executive indicated that his company samples at least 30 dosage units and assays between 20 to 30 samples per validation batch and approximately 10 samples per routine production batch for compendial testing (Company 1, 2003). Thus, ERG estimated that, on average, companies sample 30 dosage units and assay 25 units per validation and 10 units per routine production batch for compendial testing. ERG further estimated that 6 and 2 hours of production operator time is needed to prepare for and obtain the samples for validation and routine production batches, respectively. The estimate reflects the labor time needed to label the sample vials, obtain dosage unit samples from production bins, and transfer the samples to the laboratory for analytical testing. ERG also estimated that it takes 1/2 hour per sample assayed for a laboratory technician to document and record the test results. With an estimated per-sample laboratory testing cost of $128 (see Section 1.4.2), the compendial testing costs are estimated at $3,315 per validation batch and at $1,325 per routine production batch in the model.

[9] Weight variation requirements may be applied where the product is a liquid-filled soft capsule or where the product to be tested contains 50 milligram or more of an active ingredient comprising 50 percent or more of the dosage-form unit by weight (USP <905>, 1990).

BUWG Recommendation. BUWG recommends in-process dosage unit analysis in lieu of blend *and* compendial testing for routine production batches. To utilize the BUWG recommendation, however, manufacturers must first demonstrate that testing of in-process stratified dosage unit samples provides at least equivalent control (i.e., sensitivity to lack of uniformity) to compendial testing of finished dosage units for each validation batch. Only upon demonstration of such a relationship is the manufacturer allowed to cease compendial testing all together. If the relationship between in-process and compendial testing cannot be demonstrated, then the manufacturer must conduct both in-process stratified and finished product compendial testing (see Section 1.2).

In the model, ERG judged that manufacturers will need to conduct compendial testing on all validation batches (at a cost of $3,315 per batch) to be able to eliminate it during routine production. ERG further assumed that for 95 percent of products, manufacturers will demonstrate the necessary relationship between in-process and compendial testing and be able to cease compendial testing for routine production. Thus, ERG estimated the cost of compendial testing for routine batches at $66 ($1,325 × 0.05) under the BUWG proposal.

3.1.3 In-process Content Uniformity (CU) Testing

In-process Content Uniformity (CU) testing refers to the BUWG-proposed method of taking dosage unit samples at predefined locations throughout the compression and filling process and assaying them (according to USP <905>) for content uniformity. Unlike compendial testing, where randomly sampled *finished* dosage units are assayed for dose uniformity, in-process CU testing requires a stratified sampling plan where *in-process* dosage units (collected at different locations) are assayed for dose uniformity. The sampling locations must be representative of the compression and filling process and include samples from the beginning and the end of the batch (PQRI/BUWG, 2002). Further, BUWG recommends the use of in-process

CU testing in conjunction with blend testing for validation batches and in lieu of blend and compendial testing for routine production batches.

Current practice. Currently, the in-process CU testing recommendations of BUWG are not officially endorsed by FDA or other industry organizations. Nonetheless, various companies contacted for the study have adopted in-process CU testing for their validation batches (Company 1, 2, and 4, 2003). Because the adoption of the method is completely voluntary, however, ERG did not allocate in-process CU testing costs to companies (innovator and generic) in the baseline.

BUWG Recommendation. Under BUWG recommendations, companies will need to conduct in-process CU testing for all of their validation and routine production batches. For validation batches, manufacturers will need to collect 7 in-process dosage unit samples from at least 20 locations across filling and compression operations and assay initially at least 3 samples per location (a total of 60 samples). The manufacturer may then cease additional in-process CU testing for a given validation batch provided that (1) the RSD of all individual samples are less than or equal to 6.0 percent, (2) each location mean is within 90 to 110 percent of target potency, and (3) all individual samples are within 75 to 125 percent target potency. If any of these conditions are violated, BUWG requires the manufacturer to assay at least 4 more in-process dosage units from each location and reevaluate the results.

For those validation batches that do not meet the BUWG acceptance criteria after the second stage testing, further reformulation research and development is recommended. ERG did not, however, allocate any process development costs companies (generic and innovator) will need to incur to arrive at process parameters upon failing to meet the BUWG acceptance criteria in the analysis. These are a part of product research and development costs and hence are not attributable to the BUWG proposal.

For the analysis, ERG forecasts that, on average, manufacturers will need to assay 3 dosage units per location (a total of 60 samples) for in-process CU testing at a cost of $128 per sample (see Section 1.4.2). Because the collection of in-process dosage units is not as labor intensive as blend sampling, ERG allocated 4 hours of production operator time for preparing for and obtaining samples. Assuming it takes an hour to record and properly document assay results, the cost of in-process CU testing per validation batch is estimated at $7,761.

Unlike validation, during routine production, manufacturers will need to sample in-process dosage units across 10 (rather than 20) locations during the compression and filling operations. For readily-compliant batches, manufacturers will then need to assay one sample per location (a total of 10 units) to meet the BUWG requirements. Manufacturers will, however, need to assay as much as 3 dosage units per location (a total of 30 samples) for marginally-compliant routine production batches.

As part of the research on blend uniformity, BUWG conducted a survey in which it asked manufacturers to supply content uniformity data for blends, in-process dosage unit samples, and finished dosage forms for their products. The objective of the data collection was to check the validity of the recommended sampling plans and acceptance criteria BUWG derived through computer simulations. BUWG received responses from eight pharmaceutical companies that submitted content uniformity data on a total of 149 batches. Of the 149 batches, however, only 88 had data from at least 10 locations. Among the 88 batches, 86 batches readily passed the BUWG acceptance criteria whereas the remaining 2 batches marginally passed (PQRI/BUWG, 2002). Thus, based on the results of the BUWG data-mining effort, ERG estimated the probability of a routine production batch being readily compliant at 97.7 percent (86 out of 88) and marginally compliant at 2.3 percent (2 out of 88) at any given period. Assuming that it takes half the labor hours to collect samples of in-process dosage units during production, ERG further estimated the expected cost of in-process CU testing per routine production batch at $1,394.

3.1.4 Out-of-Specification (OOS) Analysis and Resolution

An out-of-specification (OOS) result occurs when an individual test result does not meet the specifications outlined in official compendia, the firm's (A)NDA or by the manufacturer. For example, the quantity of active ingredient might not fall within 85 to 115 percent of the label claim. FDA requires manufacturers to investigate each OOS result shortly after its occurrence and to document each step of the review. The OOS investigation must follow the firm's standard operating procedure (SOP) manual. The failure investigation should determine the cause of the OOS so that the manufacturer can properly decide whether to release, reject, or reprocess the batch in question. Even if a batch is rejected, the manufacturer still needs to conduct a full failure investigation to determine if the result suggests problems for other batches of the same drug product or other products (FDA, 1998).

When faced with an OOS result, the manufacturer must determine whether the result originates with a:

- Laboratory error,
- Nonprocess-related or operator error, or
- Process-related or manufacturing error.

Laboratory errors can result from an analyst's mistake or from malfunctioning laboratory equipment. Such errors include calculation mistakes, use of incorrect standards for comparison, and mismeasurement. Manufacturers can often readily identify and resolve these errors (Company 2, 2003).

Nonprocess-related errors are mainly due to human and mechanical errors sometimes generated during the manufacturing process, such as errors in operating equipment or equipment malfunctions. In contrast, process-related problems, such as incorrect mixing time and particle segregation in the powder blend, might occur even when the operators and manufacturing equipment are functioning properly (United States v. Barr Laboratories, 1993).

On average, the extent of the failure investigation varies with the type of error. While nonprocess-related errors and errors in operating merit an in-depth investigation, laboratory errors are relatively easy to address. In the model, ERG classified the type of OOS analysis into two categories: quickly-resolved and not-quickly-resolved problems. All OOS investigations require at least a report by the analyst to the supervisor of the anomalous result and an informal laboratory inspection by two technicians. In the laboratory, the technicians should (1) review the notebook that contained the result, (2) discuss the testing procedures along with any required calculations, and (3) examine the instrument used (Jimenez, 1997). ERG judged that for quickly-resolved problems, the failure investigation will only consist of these minimum paperwork requirements in addition to the additional samples assayed.

Typically, companies will perform an in-depth failure investigation for nonprocess- and process-related problems (not-quickly-resolved problems). Such an investigation consists of (1) the reason for the investigation, (2) a summation of the process sequences that might have caused the problem, (3) an outline of the corrective actions necessary to save the batch and prevent a similar recurrence, (4) a list of other batches and products possibly affected, the results of the investigations, and any required corrective action, and (5) comments and signatures of production and quality control personnel who conducted the investigation and approved any reprocessed material after additional testing (Jimenez, 1997).[10]

Upon completion of a failure investigation, the manufacturer may need to (BUWG, 2000):

[10] In its May 3, 1996 proposal, FDA advocates this type of failure investigation for any unexplained discrepancy, including any OOS test result (Federal Register 61, 1996).

- Repeat its blend sampling and testing,
- Perform extended compendial testing of the finished dosage form,
- Perform extended blend sampling and testing,
- Remix the blend and reconduct sampling and testing, or
- Reject the batch.

If the failure investigation indicates that a laboratory error caused the OOS result, a manufacturer will typically assay the additional samples collected (commonly referred to as retesting) and document the OOS analysis in a brief report as discussed previously. Executive of large innovator and generic companies indicated that only a small minority of OOS results are attributable to laboratory errors (i.e., quickly-resolved problems) (Company 1 and 2, 2003). Thus, ERG judged that on average, approximately 5 percent of OOS results are quickly resolved. For these, ERG allotted 30 labor hours and additional assay costs of $384 (3 additional assays at a price of $128 each) for a total of $1,235.

The cost of not-quickly-resolved problems depends upon the manufacturer's course of action. Table 3-2 provides the expected probability of each option based on the reported frequency of responses to a question in the BUWG survey of current industry practices. From the table, manufacturers are most likely to respond to an OOS result during blend testing by performing extended CU testing of the final dosage form (36.1 percent). Batch rejection (i.e., variance batch to waste option) is the least likely response at 5.6 percent. Around 14 percent of the time, however, manufacturers use an alternative course of action (i.e., "other" in the table).

In the model, ERG assumed that manufacturer responses to OOS results according to the probabilities (frequencies) of the alternative actions shown in Table 3-2. Thus, ERG estimated the expected total cost of not-quickly-resolved problems, *TCNQR*, as:

Table 3-2: Frequency of Survey Responses to the Most Common Action to a Blend Uniformity Testing Failure (Question 17 in the BUWG Survey)

	Number of Responses	
Course of Action	**Total**	**Percent of Total**
Option 1-Repeat sampling and testing	7	19.4%
Option 2-Perform extended content uniformity testing of final dosage form	13	36.1%
Option 3-Perform extended blend sampling and testing	6	16.7%
Option 4-Remix blend and resample	3	8.3%
Option 5-Variance batch to waste	2	5.6%
Option 6-Other	5	13.9%
Total	**36**	**100.0%**

Source: BUWG, 2000

$$TCNQR = LC + \sum_{i=1}^{6} p_i \times C_i$$

where

LC = Labor cost of failure investigation and reporting,

p_i = Probability of option i, where i = 1, ..., 6, and

C_i = Total cost of (labor hours and testing) option i, where i = 1, ..., 6.

Companies indicated that the time and effort involved in tracking, investigating, and documenting the cause of an OOS result (that is not due to a laboratory error) is extensive (Company 1, and 2, 2003). Thus, ERG allotted a total of 450 labor hours to the investigation and reporting of not-quickly-resolved problems, *LC*, regardless of the course of action chosen (i.e., retest, remix, or reject) at the conclusion of the investigation. ERG further estimated that the costs for the 6 different courses of action, C_i, will range from \$662 (Option 2 - Perform extended content uniformity testing of final dosage form) to \$94,785 (Option 5 - Reject the batch) as depicted in Table 3-1. The overall cost of OOS investigation for a not-quickly-resolved problem is estimated at \$21,928. The figure correlates well with the \$20,000 estimate quoted by one company executive and the \$35,000 forecast published by Mathis Instruments (Company 2, 2003, and Mathis Instruments, 2003).

Current practice. Assuming that only 5 percent of the OOS results are quickly resolved, ERG estimated the expected cost of a given OOS investigation at $20,893 (0.05 × $1,235 + 0.95 × $21,928) in the baseline for routine production batches. The OOS investigation concept is only applicable for commercial production. Hence, no OOS investigation costs were allocated for validation batches.

BUWG Recommendation. The nature of an OOS investigation is not likely to change after the adoption of BUWG recommendations. Although some companies may choose to perform extended in-process CU testing rather than compendial testing for option 2, the impact of this change is minimal. Thus, ERG allotted the same baseline OOS investigation cost of $20,893 for routine production batches under the BUWG proposal.

3.2 One-time Costs of Adopting BUWG Recommendations by Company Type

Manufacturers incur one-time costs each time there is a change in regular manufacturing procedures. Thus, solid oral drug product manufacturers will incur costs to incorporate the BUWG recommendations into their manufacturing operations. Based on its industry contacts, ERG enumerated these one-time costs into the following components:

- Planning and coordination,
- Manufacturing ticket modification, and
- Modification of sample handling logistics.

Table 3-3 presents the one-time costs innovator and generic manufacturers will incur to adopt the BUWG recommendations. Because companies have not yet adopted the BUWG recommendations, most one-time cost forecasts are uncertain. The following sections describe each of these cost components in further detail.

Table 3-3: One-time Costs Associated with the Adoption of BUWG Recommendations

	Innovator			Generic			
Element	**Small**	**Medium**	**Large**	**Small**	**Medium**	**Large**	**Source/Comment**
Planning and Coordination	**$2,903**	**$17,074**	**$59,667**	**$3,639**	**$16,094**	**$101,780**	Computed value
Statistician hours for sampling plan development	8	8	8	8	8	8	ERG estimate
Statistician hourly wage rate	$37.75	$37.75	$37.75	$37.75	$37.75	$37.75	BLS 2002 and 2001
Production operator hours to incorporate sampling plan into production	4	4	4	4	4	4	ERG estimate
Production operator hourly wage rate	$18.38	$18.38	$18.38	$18.38	$18.38	$18.38	BLS 2002 and 2001
Mid-level manager hours for review and approval	2	2	2	2	2	2	ERG estimate
Mid-level manager hourly wage rate	$45.18	$45.18	$45.18	$45.18	$45.18	$45.18	BLS 2002 and 2001
Manager hours for review and approval	0.5	0.5	0.5	0.5	0.5	0.5	ERG estimate
Manager hourly wage rate	$48.66	$48.66	$48.66	$48.66	$48.66	$48.66	BLS 2002 and 2001
Average number of products	6	35	122	7	33	208	Orange Book, 2002
Manufacturing Ticket Modification	**$971**	**$5,708**	**$19,947**	**$1,216**	**$5,380**	**$34,025**	Computed value
Production operator hours	4	4	4	4	4	4	ERG estimate
Production operator hourly wage rate	$18.38	$18.38	$18.38	$18.38	$18.38	$18.38	BLS 2002 and 2001
Mid-level manager hours	2	2	2	2	2	2	ERG estimate
Mid-level manager hourly wage rate	$45.18	$45.18	$45.18	$45.18	$45.18	$45.18	BLS 2002 and 2001
Average number of products	6	35	122	7	33	208	Orange Book, 2002
Modification of Sample Handling Logistics	**$2,799**	**$3,598**	**$5,196**	**$2,799**	**$3,598**	**$5,196**	Computed value
Laboratory technician hours for training and SOP changes	40	80	160	40	80	160	ERG estimate
Laboratory technician hourly wage rate	$19.97	$19.97	$19.97	$19.97	$19.97	$19.97	BLS 2002 and 2001
Upfront cost of sample analysis program modification and validation	$2,000	$2,000	$2,000	$2,000	$2,000	$2,000	ERG estimate

3.2.1 Planning and Coordination

BUWG recommendations require manufacturers to sample in-process dosage units across the manufacturing lot using a stratified sampling plan. The method requires manufacturers to keep track of which location a given unit dosage sample is drawn from. This differs from the current practice of collecting and handling randomly-collected finished dosage samples together for each batch. Thus, manufacturers will initially need to devise a stratified sampling plan for each product they manufacture and incorporate this into their production operation. Companies indicated that they will also need to devise a contingency plan to accommodate any foreseeable operator error (such as missing the time interval for sampling) (Company 4, 2003).

ERG allotted 8 hours of statistician and 4 hours of production operator time per product to develop a sampling plan and incorporate the plan into production, respectively. Because the sampling plan needs to be officially incorporated into a firm's standard operating procedure (SOP) manual, ERG also estimated that 2 hours of mid-level manager (typically, an industrial production manager) and 1/2 hour of manager time will be needed per product for review and approval of the change. ERG did not allocate any equipment costs (for additional vials for sample collection) as these are believed to be minimal.

Overall, the total estimated cost of planning and coordination ranges from around $2,900 to $60,000 for small to large innovator firms and from $3,600 to $102,000 for small to large generic firms. The higher planning and coordination costs for generic companies are attributable to the higher number of products manufactured. Innovator companies typically have more knowledge about their drugs given their longer development history with the drugs and the data collected during the research and development phase (Company 2, 2003). Thus, these companies are expected to incur lower costs to implement any type of manufacturing operation changes.

3.2.2 Manufacturing Ticket Modification

Each drug product has its own manufacturing ticket, which is basically a step-by-step "recipe" for product manufacturing. The ticket specifies all the manufacturing steps involved, sampling plans to be used, and any other applicable information relevant for the production of the product. Manufacturers will need to modify each ticket to reflect the change in sampling and handling of samples for routine production batches.

ERG estimated that it will take 4 hours of production operator time to modify the ticket and 2 hours of mid-level managerial time to review and approve the change per product. Overall, ERG estimated the total cost of manufacturing ticket modification from approximately $1,000 to $20,000 for small to large innovator firms and from around $1,200 to $34,000 for small to large generic firms.

3.2.3 Modification of Sample Handling Logistics

Companies indicated that they will need to change the manner in which dosage unit samples are handled in their analytical laboratories (Company 4, 2003). As will be required during sample collection, manufacturers will need to keep track of where a given dosage unit sample has been drawn during analytical testing. This will require a change in laboratory SOPs and training of laboratory personnel in the new procedures. For SOP modification and training, ERG allotted 40 hours of laboratory technician time for small, 80 hours for medium, and 160 hours for large companies. The upper-end estimate reflects the higher number of analysts employed in high-volume large-company operations.

Given that the BUWG recommended acceptance criteria differs from that provided in USP <905> for content uniformity, the analytical laboratory will also need to modify the program for evaluating assay results. A company executive described this as modifying a relatively simple spreadsheet (such as one in Microsoft Excel) to accommodate additional data points and computations. Although some companies may have more sophisticated custom applications for data analysis, ERG believes that simple changes in acceptance criteria and number of data points will be easily accommodated by these programs. Thus, ERG estimated the upfront cost of modifying and validating the sample analysis program at $2,000 for all types and sizes of companies.

Overall, the total cost of modifying sample handling logistics in the analytical laboratory is estimated at roughly $2,800 for small, $3,600 for medium-sized, and at $5,200 for large innovator and generic firms.

3.3 Per-firm Impacts

In computing the baseline costs, ERG used a reference OOS frequency of 2 percent. ERG then computed the per-firm costs under the BUWG proposal, assuming 95, 90, and 80 percent reductions in the OOS frequency attributable to the adoption of the stratified in-process sampling method, respectively. Tables 3-4 and 3-5 present the estimated costs in the baseline and after the adoption of BUWG recommendations, respectively, under the three scenarios. The per-firm baseline costs for innovator companies are considerably lower than those for generic companies because they do not conduct blend testing on routine production batches. The estimated baseline costs per firm range from $167,000 for small, to $984,000 for medium-sized, and to $3.5 million for large innovator companies. For generic companies, however, the per-firm baseline costs range from $489,000 for small, to $2.2 million for medium-sized, to $13.8 million for large companies.

With the adoption of the BUWG recommendations, the per-firm costs will increase for innovator but decrease for generic companies. The increase in costs for innovator companies is mainly attributable to the tighter requirements for validation batches under the BUWG proposal. For generic companies, however, the increased costs from tighter requirements for validation are

Table 3-4: Unit (Per-firm) Costs Under Current Industry Practice

	Innovator			Generic		
Element	**Small**	**Medium**	**Large**	**Small**	**Medium**	**Large**
Validation	**$12,439**	**$73,540**	**$306,769**	**$16,809**	**$71,439**	**$571,215**
Blend Testing	$2,626	$15,523	$64,755	$3,548	$15,080	$120,576
Compendial Testing (USP <905>)	$9,813	$58,017	$242,014	$13,261	$56,359	$450,638
In-process Content Uniformity (CU) Testing	NA	NA	NA	NA	NA	NA
Out-of-Specification (OOS) Analysis and Resolution	NA	NA	NA	NA	NA	NA
Routine Production	**$154,823**	**$910,509**	**$3,181,832**	**$472,063**	**$2,088,002**	**$13,204,834**
Blend Testing	$0	$0	$0	$278,031	$1,229,771	$7,777,252
Compendial Testing (USP <905>)	$117,698	$692,179	$2,418,862	$147,505	$652,436	$4,126,104
In-process Content Uniformity (CU) Testing	NA	NA	NA	NA	NA	NA
Out-of-Specification (OOS) Analysis and Resolution	$37,125	$218,331	$762,971	$46,527	$205,795	$1,301,478
One-time Costs of Adopting BUWG Recommendations	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**
Planning and Coordination	NA	NA	NA	NA	NA	NA
Manufacturing Ticket Modification	NA	NA	NA	NA	NA	NA
Modification of Sample Handling Logistics	NA	NA	NA	NA	NA	NA
Total One-time Costs	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**
Total Recurring Costs	**$167,262**	**$984,050**	**$3,488,601**	**$488,872**	**$2,159,441**	**$13,776,048**
Total Annual Costs	**$167,262**	**$984,050**	**$3,488,601**	**$488,872**	**$2,159,441**	**$13,776,048**

Table 3-5: Unit (Per-firm) Costs Under BUWG Recommendations

	Innovator			Generic		
Element	**Small**	**Medium**	**Large**	**Small**	**Medium**	**Large**
Validation	**$36,926**	**$218,313**	**$910,675**	**$49,900**	**$212,075**	**$1,695,709**
Blend Testing	$4,139	$24,469	$102,073	$5,593	$23,770	$190,063
Compendial Testing (USP <905>)	$9,813	$58,017	$242,014	$13,261	$56,359	$450,638
In-process Content Uniformity (CU) Testing	$22,974	$135,826	$566,589	$31,046	$131,945	$1,055,008
Out-of-Specification (OOS) Analysis and Resolution	NA	NA	NA	NA	NA	NA
Routine Production (Scenario 1 - 95% reduction)	**$131,550**	**$773,639**	**$2,703,530**	**$164,865**	**$729,220**	**$4,611,692**
Routine Production (Scenario 2 - 90% reduction)	**$133,406**	**$784,556**	**$2,741,679**	**$167,191**	**$739,509**	**$4,676,766**
Routine Production (Scenario 1 - 80% reduction)	**$137,119**	**$806,389**	**$2,817,976**	**$171,844**	**$760,089**	**$4,806,914**
Blend Testing	NA	NA	NA	NA	NA	NA
Compendial Testing (USP <905>)	$5,885	$34,609	$120,943	$7,375	$32,622	$206,305
In-process Content Uniformity (CU) Testing	$123,809	$728,114	$2,544,439	$155,163	$686,308	$4,340,313
Out-of-Specification (OOS) Analysis and Resolution						
Scenario 1 - 95% reduction	$1,856	$10,917	$38,149	$2,326	$10,290	$65,074
Scenario 2 - 90% reduction	$3,713	$21,833	$76,297	$4,653	$20,580	$130,148
Scenario 3 - 80% reduction	$7,425	$43,666	$152,594	$9,305	$41,159	$260,296
One-time Costs of BUWG Adoption	**$6,673**	**$26,380**	**$84,810**	**$7,654**	**$25,072**	**$141,001**
Planning and Coordination	$2,903	$17,074	$59,667	$3,639	$16,094	$101,780
Manufacturing Ticket Modification	$971	$5,708	$19,947	$1,216	$5,380	$34,025
Modification of Sample Handling Logistics	$2,799	$3,598	$5,196	$2,799	$3,598	$5,196
Scenario 1 - 95% reduction						
Total One-time Costs	**$6,673**	**$26,380**	**$84,810**	**$7,654**	**$25,072**	**$141,001**
Total Recurring Costs	**$168,476**	**$991,952**	**$3,614,205**	**$214,765**	**$941,295**	**$6,307,402**
Total Annual Costs	**$169,426**	**$995,707**	**$3,626,280**	**$215,854**	**$944,864**	**$6,327,477**
Scenario 2 - 90% reduction						
Total One-time Costs	**$6,673**	**$26,380**	**$84,810**	**$7,654**	**$25,072**	**$141,001**
Total Recurring Costs	**$170,332**	**$1,002,868**	**$3,652,354**	**$217,091**	**$951,584**	**$6,372,475**
Total Annual Costs	**$171,282**	**$1,006,624**	**$3,664,429**	**$218,181**	**$955,154**	**$6,392,551**
Scenario 3 - 80% reduction						
Total One-time Costs	**$6,673**	**$26,380**	**$84,810**	**$7,654**	**$25,072**	**$141,001**
Total Recurring Costs	**$174,045**	**$1,024,701**	**$3,728,651**	**$221,744**	**$972,164**	**$6,502,623**
Total Annual Costs	**$174,995**	**$1,028,457**	**$3,740,726**	**$222,833**	**$975,734**	**$6,522,699**

Table 3-6: Unit (Per-firm) Costs (Savings) From Adoption of BUWG Recommendations

	Innovator			Generic		
Element	**Small**	**Medium**	**Large**	**Small**	**Medium**	**Large**
Validation	**$24,487**	**$144,772**	**$603,906**	**$33,091**	**$140,636**	**$1,124,495**
Blend Testing	$1,513	$8,946	$37,318	$2,045	$8,690	$69,487
Compendial Testing (USP <905>)	$0	$0	$0	$0	$0	$0
In-process Content Uniformity (CU) Testing	$22,974	$135,826	$566,589	$31,046	$131,945	$1,055,008
Out-of-Specification (OOS) Analysis and Resolution	NA	NA	NA	NA	NA	NA
Routine Production (Scenario 1 - 95% reduction)	**($23,274)**	**($136,870)**	**($478,302)**	**($307,198)**	**($1,358,782)**	**($8,593,142)**
Routine Production (Scenario 2 - 90% reduction)	**($21,417)**	**($125,954)**	**($440,154)**	**($304,872)**	**($1,348,493)**	**($8,528,068)**
Routine Production (Scenario 1 - 80% reduction)	**($17,705)**	**($104,121)**	**($363,857)**	**($300,219)**	**($1,327,913)**	**($8,397,920)**
Blend Testing	NA	NA	NA	($278,031)	($1,229,771)	($7,777,252)
Compendial Testing (USP <905>)	($111,813)	($657,570)	($2,297,919)	($140,130)	($619,814)	($3,919,798)
In-process Content Uniformity (CU) Testing	$123,809	$728,114	$2,544,439	$155,163	$686,308	$4,340,313
Out-of-Specification (OOS) Analysis and Resolution						
Scenario 1 - 95% reduction	($35,269)	($207,414)	($724,822)	($44,201)	($195,505)	($1,236,404)
Scenario 2 - 90% reduction	($33,413)	($196,498)	($686,674)	($41,874)	($185,216)	($1,171,331)
Scenario 3 - 80% reduction	($29,700)	($174,665)	($610,377)	($37,222)	($164,636)	($1,041,183)
One-time Costs of BUWG Adoption	**$6,673**	**$26,380**	**$84,810**	**$7,654**	**$25,072**	**$141,001**
Planning and Coordination	$2,903	$17,074	$59,667	$3,639	$16,094	$101,780
Manufacturing Ticket Modification	$971	$5,708	$19,947	$1,216	$5,380	$34,025
Modification of Sample Handling Logistics	$2,799	$3,598	$5,196	$2,799	$3,598	$5,196
Scenario 1 - 95% reduction						
Total One-time Costs (Savings)	**$6,673**	**$26,380**	**$84,810**	**$7,654**	**$25,072**	**$141,001**
Total Recurring Costs (Savings)	**$1,214**	**$7,902**	**$125,604**	**($274,108)**	**($1,218,147)**	**($7,468,647)**
Total Annual Costs (Savings)	**$2,164**	**$11,658**	**$137,679**	**($273,018)**	**($1,214,577)**	**($7,448,572)**
Scenario 2 - 90% reduction						
Total One-time Costs (Savings)	**$6,673**	**$26,380**	**$84,810**	**$7,654**	**$25,072**	**$141,001**
Total Recurring Costs (Savings)	**$3,070**	**$18,818**	**$163,753**	**($271,781)**	**($1,207,857)**	**($7,403,573)**
Total Annual Costs (Savings)	**$4,020**	**$22,574**	**$175,828**	**($270,692)**	**($1,204,287)**	**($7,383,498)**
Scenario 3 - 80% reduction						
Total One-time Costs (Savings)	**$6,673**	**$26,380**	**$84,810**	**$7,654**	**$25,072**	**$141,001**
Total Recurring Costs (Savings)	**$6,782**	**$40,651**	**$240,050**	**($267,129)**	**($1,187,278)**	**($7,273,425)**
Total Annual Costs (Savings)	**$7,732**	**$44,407**	**$252,125**	**($266,039)**	**($1,183,708)**	**($7,253,350)**

offset by savings from the elimination of routine blend testing. The estimated annual incremental costs of the BUWG proposal range from \$2,200 to \$7,700 for small, \$11,700 to \$44,400 for medium-sized, and from \$137,700 to \$252,100 for large innovator companies under the three scenarios. In contrast, the net annual cost savings to generic firms will range from \$273,000 to \$266,000 for small, from \$1.18 million to \$1.21 million for medium-sized, and from \$7.3 million to \$7.5 million for large firms under the three scenarios (see Table 3-6).

The magnitude of per-firm costs and savings are sensitive to the average manufacturing batch value estimated at \$94,782 for all firms (innovator and generic). Should the figure be adjusted to reflect a higher per-batch value for innovator firms, the per-firm costs for innovator companies under the BUWG proposal will decline as savings from reductions in OOS result frequency will partially (or completely) offset the increase in costs for validation due to tighter testing requirements. In contrast, a lower average manufacturing batch value for generic firms will result in the reduction of per-firm savings generic companies are expected to realize as the magnitude of savings from expected OOS result frequency reduction and elimination of routine blend testing declines.

3.4 Total Impacts

Tables 3-7 and 3-8 present the total baseline costs and costs under the BUWG proposal by type of company, respectively. The total annual baseline costs range from \$12.7 million for small, to \$10.4 million for medium-sized, to \$42.3 million for large innovator firms. Further, generic industry annual costs range from \$44.9 million for small, to \$27.6 million for medium-sized, and to \$202.2 million for large firms. Overall, the baseline costs (innovator and generic combined) for testing and OOS analysis are \$340.2 million.

Table 3-7: Total Industry Costs Under Current Industry Practice

	Innovator			Generic			
Element	**Small**	**Medium**	**Large**	**Small**	**Medium**	**Large**	**Total**
Validation	**$944,848**	**$777,725**	**$3,723,805**	**$1,544,063**	**$913,633**	**$8,385,128**	**$16,289,203**
Blend Testing	$199,446	$164,168	$786,050	$325,933	$192,857	$1,769,998	**$3,438,451**
Compendial Testing (USP <905>)	$745,402	$613,557	$2,937,755	$1,218,130	$720,776	$6,615,130	**$12,850,751**
In-process Content Uniformity (CU) Testing	NA	NA	NA	NA	NA	NA	**NA**
Out-of-Specification (OOS) Analysis and Resolution	NA	NA	NA	NA	NA	NA	**NA**
Routine Production	**$11,760,301**	**$9,629,060**	**$38,623,608**	**$43,362,715**	**$26,703,321**	**$193,839,992**	**$323,918,998**
Blend Testing	NA	NA	NA	$25,539,341	$15,727,457	$114,165,953	**$155,432,751**
Compendial Testing (USP <905>)	$8,940,302	$7,320,110	$29,362,064	$13,549,512	$8,343,965	$60,569,023	**$128,084,976**
In-process Content Uniformity (CU) Testing	NA	NA	NA	NA	NA	NA	**NA**
Out-of-Specification (OOS) Analysis and Resolution	$2,819,999	$2,308,950	$9,261,544	$4,273,862	$2,631,899	$19,105,016	**$40,401,271**
One-time Costs of Adopting the BUWG Recommendations	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**
Planning and Coordination	NA	NA	NA	NA	NA	NA	**NA**
Manufacturing Ticket Modification	NA	NA	NA	NA	NA	NA	**NA**
Modification of Sample Handling Logistics	NA	NA	NA	NA	NA	NA	**NA**
Total One-time Costs	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**
Total Recurring Costs	**$12,705,149**	**$10,406,785**	**$42,347,413**	**$44,906,778**	**$27,616,954**	**$202,225,121**	**$340,208,200**
Total Annual Costs	**$12,705,149**	**$10,406,785**	**$42,347,413**	**$44,906,778**	**$27,616,954**	**$202,225,121**	**$340,208,200**

Table 3-8: Total Industry Costs Under BUWG Recommendations

	Innovator			Generic			
Element	**Small**	**Medium**	**Large**	**Small**	**Medium**	**Large**	**Total**
Validation	**$2,804,878**	**$2,308,756**	**$11,054,498**	**$4,583,710**	**$2,712,214**	**$24,892,116**	**$48,356,172**
Blend Testing	$314,384	$258,776	$1,239,040	$513,764	$303,998	$2,790,026	**$5,419,988**
Compendial Testing (USP <905>)	$745,402	$613,557	$2,937,755	$1,218,130	$720,776	$6,615,130	**$12,850,751**
In-process Content Uniformity (CU) Testing	$1,745,092	$1,436,423	$6,877,702	$2,851,816	$1,687,440	$15,486,959	**$30,085,433**
Out-of-Specification (OOS) Analysis and Resolution	NA	NA	NA	NA	NA	NA	**NA**
Routine Production (Scenario 1 - 95% reduction)	**$9,992,459**	**$8,181,592**	**$32,817,597**	**$15,144,113**	**$9,325,941**	**$67,697,210**	**$143,158,913**
Routine Production (Scenario 2 - 90% reduction)	**$10,133,459**	**$8,297,040**	**$33,280,674**	**$15,357,807**	**$9,457,536**	**$68,652,461**	**$145,178,977**
Routine Production (Scenario 1 - 80% reduction)	**$10,415,459**	**$8,527,935**	**$34,206,829**	**$15,785,193**	**$9,720,726**	**$70,562,963**	**$149,219,104**
Blend Testing	NA	NA	NA	NA	NA	NA	**NA**
Compendial Testing (USP <905>)	$447,015	$366,006	$1,468,103	$677,476	$417,198	$3,028,451	**$6,404,249**
In-process Content Uniformity (CU) Testing	$9,404,444	$7,700,139	$30,886,417	$14,252,945	$8,777,148	$63,713,508	**$134,734,601**
Out-of-Specification (OOS) Analysis and Resolution							
Scenario 1 - 95% reduction	$141,000	$115,447	$463,077	$213,693	$131,595	$955,251	**$2,020,064**
Scenario 2 - 90% reduction	$282,000	$230,895	$926,154	$427,386	$263,190	$1,910,502	**$4,040,127**
Scenario 3 - 80% reduction	$564,000	$461,790	$1,852,309	$854,772	$526,380	$3,821,003	**$8,080,254**
One-time Costs of BUWG Adoption	**$506,866**	**$278,982**	**$1,029,487**	**$703,072**	**$320,645**	**$2,069,825**	**$4,908,877**
Planning and Coordination	$220,534	$180,568	$724,286	$334,231	$205,824	$1,494,080	**$3,159,522**
Manufacturing Ticket Modification	$73,725	$60,364	$242,130	$111,734	$68,807	$499,473	**$1,056,233**
Modification of Sample Handling Logistics	$212,608	$38,050	$63,071	$257,107	$46,014	$76,272	**$693,122**
Scenario 1 - 95% reduction							
Total One-time Costs	**$506,866**	**$278,982**	**$1,029,487**	**$703,072**	**$320,645**	**$2,069,825**	**$4,908,877**
Total Recurring Costs	**$12,797,337**	**$10,490,349**	**$43,872,095**	**$19,727,824**	**$12,038,155**	**$92,589,326**	**$191,515,086**
Total Annual Costs	**$12,869,504**	**$10,530,070**	**$44,018,671**	**$19,827,925**	**$12,083,807**	**$92,884,023**	**$192,213,999**
Scenario 2 - 90% reduction							
Total One-time Costs	**$506,866**	**$278,982**	**$1,029,487**	**$703,072**	**$320,645**	**$2,069,825**	**$4,908,877**
Total Recurring Costs	**$12,938,337**	**$10,605,796**	**$44,335,173**	**$19,941,517**	**$12,169,750**	**$93,544,577**	**$193,535,149**
Total Annual Costs	**$13,010,504**	**$10,645,517**	**$44,481,748**	**$20,041,619**	**$12,215,402**	**$93,839,273**	**$194,234,063**
Scenario 3 - 80% reduction							
Total One-time Costs	**$506,866**	**$278,982**	**$1,029,487**	**$703,072**	**$320,645**	**$2,069,825**	**$4,908,877**
Total Recurring Costs	**$13,220,337**	**$10,836,691**	**$45,261,327**	**$20,368,903**	**$12,432,939**	**$95,455,078**	**$197,575,276**
Total Annual Costs	**$13,292,503**	**$10,876,412**	**$45,407,903**	**$20,469,005**	**$12,478,592**	**$95,749,775**	**$198,274,190**

Table 3-9: Total Industry Costs (Savings) From Adoption of BUWG Recommendations

	Innovator			Generic			
Element	**Small**	**Medium**	**Large**	**Small**	**Medium**	**Large**	**Total**
Validation	**$1,860,030**	**$1,531,032**	**$7,330,693**	**$3,039,647**	**$1,798,581**	**$16,506,987**	**$32,066,969**
Blend Testing	$114,938	$94,608	$452,991	$187,831	$111,141	$1,020,028	**$1,981,537**
Compendial Testing (USP <905>)	$0	$0	$0	$0	$0	$0	**NA**
In-process Content Uniformity (CU) Testing	$1,745,092	$1,436,423	$6,877,702	$2,851,816	$1,687,440	$15,486,959	**$30,085,433**
Out-of-Specification (OOS) Analysis and Res.	NA	NA	NA	NA	NA	NA	**NA**
Routine Production (Scenario 1 - 95% reduction)	**($1,767,842)**	**($1,447,468)**	**($5,806,011)**	**($28,218,601)**	**($17,377,380)**	**($126,142,782)**	**($180,760,084)**
Routine Production (Scenario 2 - 90% reduction)	**($1,626,842)**	**($1,332,020)**	**($5,342,934)**	**($28,004,908)**	**($17,245,785)**	**($125,187,531)**	**($178,740,021)**
Routine Production (Scenario 1 - 80% reduction)	**($1,344,842)**	**($1,101,125)**	**($4,416,779)**	**($27,577,522)**	**($16,982,595)**	**($123,277,030)**	**($174,699,894)**
Blend Testing	NA	NA	NA	($25,539,341)	($15,727,457)	($114,165,953)	**($155,432,751)**
Compendial Testing (USP <905>)	($8,493,287)	($6,954,105)	($27,893,961)	($12,872,036)	($7,926,767)	($57,540,572)	**($121,680,727)**
In-process Content Uniformity (CU) Testing	$9,404,444	$7,700,139	$30,886,417	$14,252,945	$8,777,148	$63,713,508	**$134,734,601**
Out-of-Specification (OOS) Analysis and Res.							
Scenario 1 - 95% reduction	($2,678,999)	($2,193,502)	($8,798,467)	($4,060,169)	($2,500,304)	($18,149,765)	**($38,381,207)**
Scenario 2 - 90% reduction	($2,537,999)	($2,078,055)	($8,335,390)	($3,846,476)	($2,368,710)	($17,194,514)	**($36,361,144)**
Scenario 3 - 80% reduction	($2,255,999)	($1,847,160)	($7,409,236)	($3,419,090)	($2,105,520)	($15,284,013)	**($32,321,017)**
One-time Costs of BUWG Adoption	**$506,866**	**$278,982**	**$1,029,487**	**$703,072**	**$320,645**	**$2,069,825**	**$4,908,877**
Planning and Coordination	$220,534	$180,568	$724,286	$334,231	$205,824	$1,494,080	**$3,159,522**
Manufacturing Ticket Modification	$73,725	$60,364	$242,130	$111,734	$68,807	$499,473	**$1,056,233**
Modification of Sample Handling Logistics	$212,608	$38,050	$63,071	$257,107	$46,014	$76,272	**$693,122**
Scenario 1 - 95% reduction							
Total One-time Costs (Savings)	**$506,866**	**$278,982**	**$1,029,487**	**$703,072**	**$320,645**	**$2,069,825**	**$4,908,877**
Total Recurring Costs (Savings)	**$92,188**	**$83,564**	**$1,524,682**	**($25,178,954)**	**($15,578,799)**	**($109,635,795)**	**($148,693,115)**
Total Annual Costs (Savings)	**$164,355**	**$123,284**	**$1,671,258**	**($25,078,853)**	**($15,533,147)**	**($109,341,098)**	**($147,994,201)**
Scenario 2 - 90% reduction							
Total One-time Costs (Savings)	**$506,866**	**$278,982**	**$1,029,487**	**$703,072**	**$320,645**	**$2,069,825**	**$4,908,877**
Total Recurring Costs (Savings)	**$233,188**	**$199,011**	**$1,987,759**	**($24,965,261)**	**($15,447,204)**	**($108,680,544)**	**($146,673,051)**
Total Annual Costs (Savings)	**$305,355**	**$238,732**	**$2,134,335**	**($24,865,160)**	**($15,401,552)**	**($108,385,848)**	**($145,974,138)**
Scenario 3 - 80% reduction							
Total One-time Costs (Savings)	**$506,866**	**$278,982**	**$1,029,487**	**$703,072**	**$320,645**	**$2,069,825**	**$4,908,877**
Total Recurring Costs (Savings)	**$515,188**	**$429,906**	**$2,913,914**	**($24,537,875)**	**($15,184,014)**	**($106,770,043)**	**($142,632,924)**
Total Annual Costs (Savings)	**$587,354**	**$469,627**	**$3,060,489**	**($24,437,773)**	**($15,138,362)**	**($106,475,346)**	**($141,934,010)**

Under the BUWG proposal, the net annual industry costs for innovator firms range from $164, 400 to $587,400 for small, from $123,300 to $469,600 for medium-sized, and from $1.7 million to $3.1 million for large firms. The generic industry, on the other hand, is estimated to realize net annual cost savings ranging from $24.4 million to $25.1 million for small, from $15.1 million to $15.5 million for medium-sized, and from $106.5 million to $109.3 million for large firms under the three different scenarios. The total cost savings to the generic industry under the BUWG proposal are expected to range from $146.0 million to $150.0 million. The innovator industry is expected to incur between $2.0 and $4.1 million to adopt the BUWG recommendations. Overall, the net annual savings to the solid oral drug product industry is approximately $141.9 million under the least optimistic scenario of 80 percent reduction in OOS result frequency and is $148.0 million under the best-case scenario of 95 percent reduction in OOS result frequency.

As discussed in the previous section, the magnitude of total industry costs and savings are also dependent on the estimated average manufacturing batch value per firm. An increase in this value for innovator firms will decrease total costs for the innovator industry sector under the BUWG proposal as savings in OOS result frequency reduction will partially (or completely) offset increased costs for validation. In contrast, a lower average manufacturing batch value for generic companies will reduce the total savings attributable to the generic industry sector. The net impact of these changes across the industry as a whole (innovator and generic) are likely to be minimal. Such changes will impact the allocation of costs/savings between the innovator and generic industry sectors, however.

SECTION FOUR

SENSITIVITY ANALYSIS

The economic impact estimates of the adoption of BUWG recommendations are sensitive to assumptions on (1) the average number of routine production batches per product manufactured by a company annually and (2) the expected percentage reduction in OOS result frequency. To characterize the degree of uncertainty surrounding the economic impact estimates, ERG conducted a sensitivity analysis. Section 4.1 presents the economic impact estimates under different assumptions on the average number of routine production batches per product. Section 4.2 depicts the variation in economic impact estimates under different values of expected OOS frequency reduction. Finally, Section 4.3 summarizes the results of the sensitivity analysis.

4.1 Average Annual Number of Routine Production Batches per Product

The scale of commercial production for a given firm can potentially vary from one batch per day for high-volume products to as low as 2 to 3 batches a year for low-volume products. Thus, the total number of routine production batches manufactured by a firm depends on the firm's high-, medium-, and low-volume product mix, as well as the total number of products it manufactures. In the model, the assumption on the number of routine production batches manufactured per product impacts the average value per batch estimates as well as the estimates of the total number of routine production batches manufactures per year by firm size.

Table 4-1 presents the range of economic impact estimates under different assumptions on the average number of routine production batches and expected OOS result frequencies. Assuming an OOS result frequency reduction of 95 percent (Scenario 1), the magnitude of cost savings to be realized by the solid oral drug product industry ranges from $18.0 million to as high

Table 4-1: Industry-wide Economic Impacts Under Different Assumptions on the Average Number of Routine Production Batches (RPB) per Product and Reduction in Expected OOS Result Frequency

Percent Reduction in OOS Frequency	Costs (Savings) by Average Number of Routine Production Batches (RPB) per Product				
	RPB=3	RPB=5	RPB=10	RPB=15	RPB=20
0.0%	$841,665	($17,567,730)	($63,590,482)	($109,612,994)	($155,635,440)
5.0%	($150,302)	($18,731,047)	($65,182,173)	($111,633,057)	($158,083,877)
10.0%	($1,142,269)	($19,894,364)	($66,773,863)	($113,653,121)	($160,532,314)
15.0%	($2,134,237)	($21,057,681)	($68,365,553)	($115,673,184)	($162,980,750)
20.0%	($3,126,204)	($22,220,998)	($69,957,244)	($117,693,248)	($165,429,187)
25.0%	($4,118,171)	($23,384,315)	($71,548,934)	($119,713,311)	($167,877,623)
30.0%	($5,110,138)	($24,547,632)	($73,140,625)	($121,733,375)	($170,326,060)
35.0%	($6,102,105)	($25,710,949)	($74,732,315)	($123,753,439)	($172,774,497)
40.0%	($7,094,073)	($26,874,266)	($76,324,005)	($125,773,502)	($175,222,933)
45.0%	($8,086,040)	($28,037,583)	($77,915,696)	($127,793,566)	($177,671,370)
50.0%	($9,078,007)	($29,200,900)	($79,507,386)	($129,813,629)	($180,119,806)
55.0%	($10,069,974)	($30,364,217)	($81,099,077)	($131,833,693)	($182,568,243)
60.0%	($11,061,942)	($31,527,534)	($82,690,767)	($133,853,756)	($185,016,680)
65.0%	($12,053,909)	($32,690,851)	($84,282,457)	($135,873,820)	($187,465,116)
70.0%	($13,045,876)	($33,854,168)	($85,874,148)	($137,893,883)	($189,913,553)
75.0%	($14,037,843)	($35,017,485)	($87,465,838)	($139,913,947)	($192,361,989)
80.0%	($15,029,811)	($36,180,802)	($89,057,529)	($141,934,010)	($194,810,426)
85.0%	($16,021,778)	($37,344,119)	($90,649,219)	($143,954,074)	($197,258,863)
90.0%	($17,013,745)	($38,507,436)	($92,240,910)	($145,974,138)	($199,707,299)
95.0%	($18,005,712)	($39,670,753)	($93,832,600)	($147,994,201)	($202,155,736)
100.0%	($18,997,679)	($40,834,070)	($95,424,290)	($150,014,265)	($204,604,172)

as $202.2 million as the average number of routine production batches manufactured per firm varies from 3 per product to 20 per product (the last highlighted row in the table).[11] Under Scenario 2 (an OOS result frequency reduction of 90 percent), the cost savings range from $17.0 million to $199.7 million as the average number of routine production batches per firm varies from 3 to 20 per product. Finally, an expected OOS frequency reduction of 80 percent (Scenario 3) yields the lowest savings among the three scenarios considered with a range of $15.0 million to $194.8 million. Thus, as expected, there is a direct relationship between economic impacts and volume of commercial production (higher production volumes correspond to higher cost savings). Under all of these scenarios, however, the innovator drug manufacturers will incur costs whereas generic drug manufacturers will accrue savings.

4.2 Expected Reduction in OOS Result Frequency

One of the uncertainties is the expected percentage reduction in OOS batch frequencies as a result of the adoption of BUWG recommendations. The adoption of BUWG recommendations is expected to improve total process and blending operation control due to tightened testing during validation. This improved control is likely to lead to fewer problems (i.e, fewer OOS batches, product recalls) during manufacturing. Additionally, given the inherent sampling error associated with thief sampling of blends, companies judged that the elimination of routine blend sampling may entirely eliminate those OOS results attributable to blend sampling errors.

Although it is not possible to forecast the expected reduction in OOS result frequency ex ante, it is possible to characterize the degree of uncertainty associated with the impact estimates via a sensitivity analysis. From Table 4-1, the industry-wide cost savings estimate ranges from $109.6 million for no reduction in OOS result frequency to $150.0 million for a 100 percent

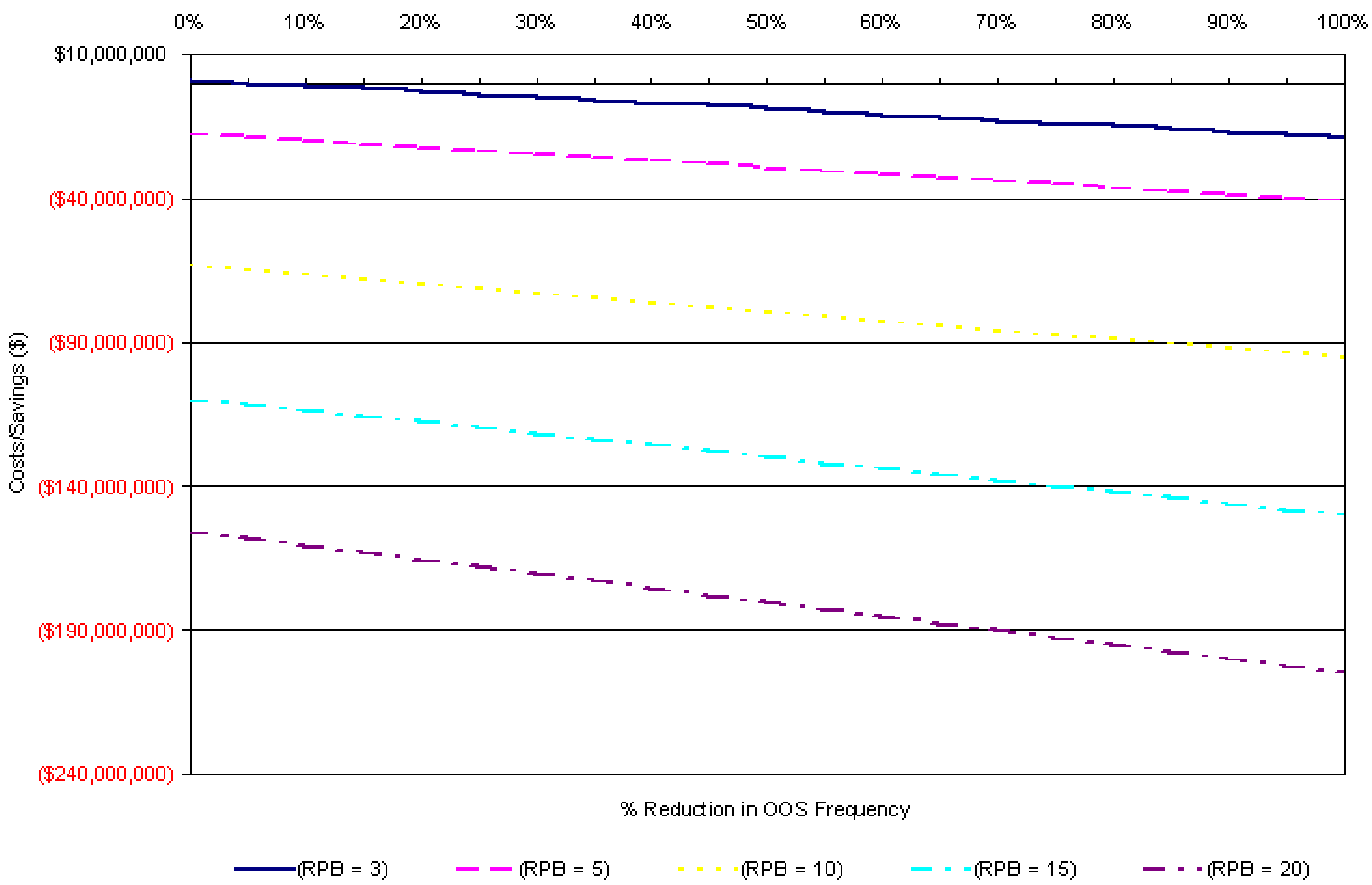
[11] The low-end of the range (an average of 3 batches per product) is not very likely but is provided for exposition purposes only.

reduction in OOS result frequency (refer to the highlighted column in the table). The overall cost savings increase approximately linearly with decreases in expected OOS results under the BUWG proposal.

4.3 Summary of Sensitivity Analysis Results

Figure 4-1 graphically depicts the relationship between OOS result frequency reductions and economic impact estimates for different values of average routine production batches per product. Even for very low production volumes (i.e., small average number of routine production batch estimates) and reductions in OOS result frequencies, the adoption of BUWG recommendations results in net overall savings to the solid oral drug product manufacturing industry. As indicated in Section Three, however, the cost savings accrue to generic manufacturers while innovator firms incur incremental costs.

Figure 4-1: Sensitivity Analysis Overview



GLOSSARY

Blend. An intermediate stage or final blend for compression, encapsulation, or other final procesing, such as sachet filling.

Blend uniformity analysis (BUA) or testing. Any procedure used in removing samples of blend and analyzing a part or whole of the sample for content of active ingredient(s).

Compendial testing. Testing of finished dosage units for content of active ingredient(s) according to USP <905>.

In-process content uniformity (CU) testing. Sampling of in-process dosage units throughout the compression or filling process (as recommended by BUWG) and then testing for content of active ingredients according to USP <905>.

Marginally-compliant. Products for which ANDA exhibit and validation batches have one or more relative standard deviation (RSD) values of greater than 4.0 but less than or equal to 6.0 percent for in-process dosage units, but which comply with the BUWG acceptance criteria for mean and individual values.

Not-quickly-resolved problem. An operator/equipment error (nonprocess-related) or a manufacturing error (process-related) yielding an OOS result. For example, manufacturing equipment might malfunction or an operator might fail to add the proper amount of an active ingredient resulting in a nonprocess-related error. In contrast, process-related problems, such as incorrect mixing time, occur even thought the operators and equipment function properly.

Out-of-specification (OOS) result. A batch with blend uniformity and/or compendial test results that fall outside the specifications or acceptance criteria established in new and/or abbreviated new drug applications, official compendia, such as the U.S. Pharmacopeia (USP), or by the manufacturer.

Quickly-resolved problem. An OOS result due to a laboratory error resulting from an analyst's mistake or malfunctioning laboratory equipment.

Readily-compliant. Products with relative standard deviation (RSD) values of less than or equal to 4.0 percent for in-process dosage units, with all mean results within 90.0 and 110.0 percent and all individual results between 75.0 and 125.0 percent, for each exhibit and validation batch.

Representative batch. A batch that adequately characterizes the majority of batches manufactured by a given company for reporting purposes.

Routine production batch. A commercial scale batch of a drug product that is manufactured in the normal course of operations and is not a batch for validation purposes.

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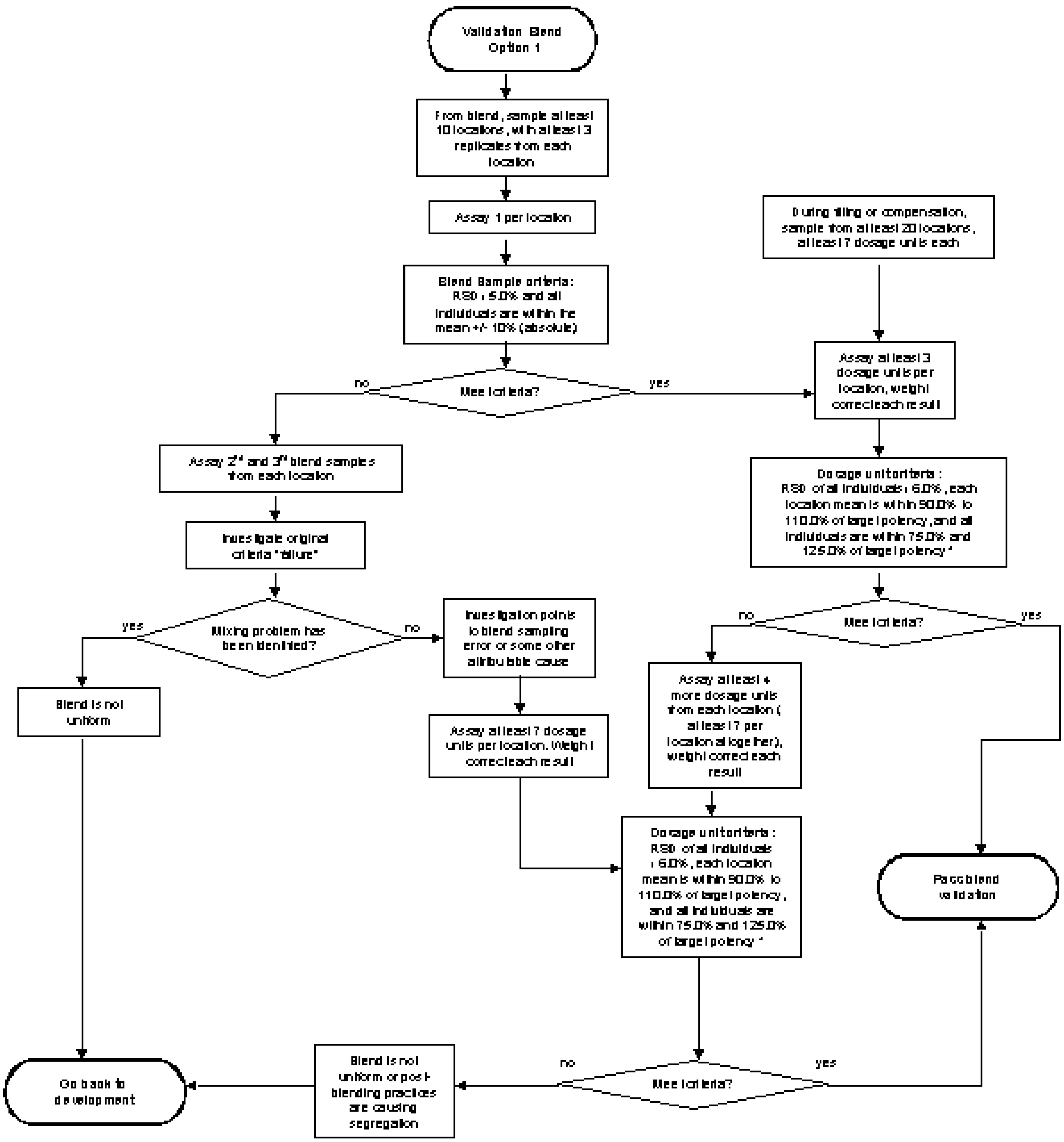
APPENDIX A

BUWG DEMONSTRATION OF ADEQUACY OF MIX AND CONTENT UNIFORMITY FOR ANDA EXHIBIT AND VALIDATION BATCHES



* When comparing individual dosage units to 75.0 – 125.0% of target potency, use the 'as is' results (not corrected for weight).

APPENDIX B

BUWG DEMONSTRATION OF ADEQUACY OF MIX AND CONTENT UNIFORMITY DURING ROUTINE MANUFACTURE